This is **Exhibit "G"** referred to in the
Affidavit of **JEANNINE RITCHOT**
Affirmed before me at the City of Ottawa,
in the Province of Ontario,
this 15th day of January 2015.

A Commissioner for Taking Affidavits

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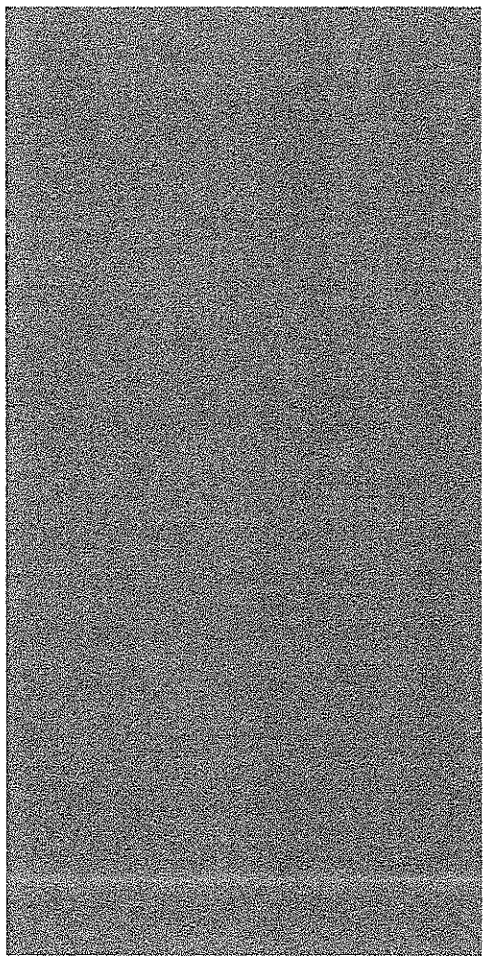
Information for Health Care Professionals

Cannabis (marihuana, marijuana) and the cannabinoids



Information for Health Care Professionals

Cannabis (marihuana, marijuana) and the cannabinoids
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 cannabis and cannabinoids for medical purposes. **Cannabis 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 cannabis 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 cannabis (marihuana) and cannabinoids. 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 cannabis (marihuana) or cannabinoids for medical purposes.

Cannabis (marijuana, marihuana) is not an approved therapeutic substance in Canada and has not been issued a notice of compliance by Health Canada authorizing sale in Canada.

Prepared by Health Canada

Date of latest version: February 2013

(May 2013) Addendum to the *Information for Health Care Professionals: Cannabis (marihuana, marijuana) and the cannabinoids* (February 2013 version)

Following the most recent update to this document (February 2013), a study was published in the Netherlands tracking data obtained from the Dutch medical cannabis program over the years 2003-2010. The study reported that in a population of over 5,000 Dutch patients using cannabis for medical purposes, the average daily dose of dried cannabis (various potencies) used was 0.68 grams per day (range: 0.65 - 0.82 grams per day) (Hazekamp and Heerdink 2013). In addition, information from Israel's medical marihuana program suggests that the average daily amount used by patients was approximately 1.5 grams of dried cannabis per day in 2011-2012 (Health Canada personal communication).

Hazekamp, A., and E.R. Heerdink (2013). The prevalence and incidence of medicinal cannabis on prescription in The Netherlands. Eur. J. Clin. Pharmacol. Published online April 16, 2013.

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List of Abbreviations

2-AG: 2-arachidonoylglycerol
5-HT: 5-hydroxytryptamine
ACEA: arachidonyl-2-chloroethylamide
ACTH: adrenocorticotropic hormone
AD: Alzheimer's disease
AEA: arachidonoylethanolamide (i.e. "anandamide")
AIDS: acquired immune deficiency syndrome
ALS: amyotrophic lateral sclerosis
ApoE: apolipoprotein E
AUC: area-under-the-curve
B.I.D.: *bis in die* (i.e. twice per day)
CAMS: Cannabis in Multiple Sclerosis
CB: cannabinoid
CBC: cannabichromene
CBD: cannabidiol
CBG: cannabigerol
CBN: cannabinol
CNS: central nervous system
CINV: chemotherapy-induced nausea and vomiting
CNR1: cannabinoid receptor gene 1
CNR2: cannabinoid receptor gene 2
CI: confidence interval
CRPS: complex regional pain syndrome
CSF: cerebrospinal fluid
CUPID: Cannabinoid Use in Progressive Inflammatory Brain Disease
CYP: cytochrome P450
Δ^9-THC: delta-9-tetrahydrocannabinol
DAG: diacylglycerol
DEA: N-docosatetraenoylethanolamine
DNBSA: dinitrobenzene sulfonic acid
DSM-IV-TR: diagnostic and statistical manual of mental disorders
ECS: endocannabinoid system
FAAH: fatty acid amide hydrolase
FEV_1: forced expiratory volume in one second
FVC: forced vital capacity
HD: Huntington's disease
HEA: N-homo-γ-linolenoylethanolamine
HIV: human immunodeficiency virus
HMO: health maintenance organization
HSV: herpes simplex virus
IBD: inflammatory bowel disease
IBS: irritable bowel syndrome
IOP: intra-ocular pressure
I.P.: intraperitoneal
I.V.: intravenous
KSHV: Kaposi's sarcoma-associated herpes virus
LDL: low density lipoprotein
MAGL: monoacylglycerol lipase
MDS: macroscopic damage score
MMAR: marihuana medical access regulations
mRNA: messenger ribonucleic acid
MS: multiple sclerosis
MUSEC: MUltiple Sclerosis and Extract of Cannabis trial
NADA: N-arachidonoyl-dopamine
NAFLD: non-alcoholic fatty liver disease
NAPE: N-arachidonoylphosphatidylethanolamine

NAT: N-acyl transferase
NIDA: National Institute on Drug Abuse
nM: nanomolar
NNT: number needed to treat
OA: osteoarthritis
OEA: oleoylethanolamide
OR: odds ratio
PAH: polycyclic aromatic hydrocarbon
PASAT: paced serial addition test
PD: Parkinson's disease
PEA: palmitoylethanolamide
PET: positron emission tomography
PPAR: peroxisome proliferator- activated receptor
PTSD: post-traumatic stress disorder
Q.I.D.: *quattuor in die* (i.e. four times per day)
QOL: quality of life
RA: rheumatoid arthritis
RCT: randomized controlled trial
REM: rapid eye movement
RGC: retinal ganglion cells
S.C.: subcutaneous
SCI: spinal cord injury
SNP: single nucleotide polymorphism
SPECT: single-photon emission computed tomography
THC: delta-9-tetrahydrocannabinol
THCA: tetrahydrocannabinolic acid
THCV: tetrahydrocannabivarin
T.I.D.: *ter in die* (i.e. three times per day)
TNBSA: trinitrobenzene sulfonic acid
TRPV1: transient receptor potential vanilloid channel 1
TS: Tourette's syndrome
μM: micromolar
VSV: vesicular stomatitis virus
WHO: World Health Organization

Author: Hanan Abramovici Ph.D.

Affiliations:
Research, Synthesis, and Dissemination Division, Office of Research and Surveillance, Controlled Substances and Tobacco Directorate, Health Canada, Ottawa, ON, Canada K1A 0K9
Email: hanan.abramovici@hc-sc.gc.ca

Acknowledgements
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Donald I. Abrams, M.D.
Chief, Hematology-Oncology
San Francisco General Hospital
Integrative Oncology
UCSF Osher Center for Integrative Medicine
Professor of Clinical Medicine
University of California San Francisco
San Francisco, CA 94143-0874
USA

Pierre Beaulieu, Ph.D., M.D., F.R.C.A.
Professeur agrégé
Département de pharmacologie
Faculté de médecine
Université de Montréal
Bureau R-408, Pavillon Roger-Gaudry
C.P. 6128 - Succursale Centre-ville
Montréal, Québec
H3C 3J7
Canada

Paul J. Daeninck, M.D., M.Sc., F.R.C.P.C
Chair, Symptom Management Group
Room LI 101-8, O Block
CancerCare Manitoba
St. Boniface Hospital
409 Taché Ave
Winnipeg, MB
R2H 2A6
Canada

Vincenzo di Marzo, Ph.D.
Research Director
Endocannabinoid Research Group
Institute of Biomolecular Chemistry
Consiglio Nazionale delle Ricerche
Via Campi Flegrei 34
Comprensorio Olivetti
80078 Pozzuoli (NA)
Italy

Mahmoud A. ElSohly, Ph.D.
Research Professor and Professor of Pharmaceutics
National Center for Natural Products Research and Department of Pharmaceutics
School of Pharmacy
University of Mississippi
University, MS 38677
USA

Javier Fernandez-Ruiz, Ph.D.
Full Professor of Biochemistry and Molecular Biology
Department of Biochemistry and Molecular Biology
Faculty of Medicine
Complutense University
Madrid, 28040
Spain

Tony George, M.D., F.R.C.P.C.
Clinical Director, Schizophrenia Program
Endowed Chair in Addiction Psychiatry, University of Toronto
Centre for Addiction and Mental Health
250 College Street, Suite 734
Toronto, ON
M5T 1R8
Canada

Boris Gorzalka, Ph.D.
Professor
Department of Psychology
University of British Columbia
Room 1614
2136 West Mall
Vancouver, BC
V6T 1Z4
Canada

Margaret Haney, Ph.D.
Professor of Clinical Neurobiology
Columbia University
Department of Psychiatry
1051 Riverside Drive, Unit 120
New York, NY 10032
USA

Matthew N. Hill, Ph.D.
Assistant Professor
Departments of Cell Biology and Anatomy & Psychiatry
The Hotchkiss Brain Institute
University of Calgary
Calgary, AB
T2N 4N1
Canada

Harold Kalant, M.D., Ph.D., O.C.
Professor Emeritus
Department of Pharmacology and Toxicology
University of Toronto
Room 4221, Medical Sciences Building
1 King's College Circle
Toronto, ON
M5S 1A8
Canada

Aron Lichtman, Ph.D.
Professor
Department of Pharmacology & Toxicology
Molecular Medicine Research Building, Room 3042
1220 East Broad St.
P.O. Box 980613
Richmond, Virginia 23298-0613
USA

Mary Lynch, M.D., F.R.C.P.C.
Professor of Anaesthesia, Psychiatry and Pharmacology
Dalhousie University
Director, Pain Management Unit-Capital Health
Queen Elizabeth II Health Sciences Centre
4th Floor Dickson Building
5820 University Avenue
Halifax, NS
B3H 1V7
Canada

Jason McDougall, Ph.D.
Associate Professor
Departments of Pharmacology and Anaesthesia
Dalhousie University
5850 College Street
Halifax, NS
B3H 1X5
Canada

Raphael Mechoulam, Ph.D.
Professor
Institute for Drug Research, Medical Faculty
Hebrew University
Jerusalem
91120
Israel

Richard (Rik) E. Musty, Ph.D.
Professor Emeritus of Psychology
Department of Psychology
College of Arts and Sciences
University of Vermont
Burlington, VT 05405
USA

Linda Parker, Ph.D.
Professor and Canada Research Chair
Department of Psychology
University of Guelph
Guelph, Ontario
N1G 2W1
Canada

Roger G. Pertwee, MA, D.Phil. D.Sc.
Professor of Neuropharmacology
Institute of Medical Sciences
University of Aberdeen
Aberdeen
AB25 2ZD
Scotland, United Kingdom

Keith Sharkey, Ph.D.
Professor
Department of Physiology and Biophysics and Medicine
University of Calgary
HSC 1745
3330 Hospital Drive NW
Calgary, AB
T2N 4N1
Canada

Cory Toth, B.Sc., M.D., C.S.C.N., F.R.C.P.C.
Assistant Professor of Neurosciences
Hotchkiss Brain Institute
Faculty of Medicine
University of Calgary
HMRB 155
3330 Hospital Drive NW
Calgary, AB
T2N 4N1
Canada

Mark Ware, M.D., M.R.C.P., M.Sc.
Associate Director
Allan Edwards Pain Management Unit, MUHC Pain Centre
E19.145 Montreal General Hospital
1650 Cedar Avenue
Montréal, Québec
H3G 1A4
Canada

IMPORTANT NOTE: For the sake of completeness and for contextual purposes, the content in the following document includes information on dried cannabis as well as selected cannabinoids. However, cannabis and cannabinoids should not be considered equivalent even though the information on both is presented together within the text. Cannabis is a highly complex material with hundreds of chemical constituents whereas cannabinoids are single molecules. Drawing direct comparisons between cannabis and cannabinoids must necessarily take into account differences in the route of administration, dosage, and the different pharmacokinetic and pharmacodynamic properties of these different substances.

1.0 The Endocannabinoid System

The endocannabinoid system **(Figure 1)** is an ancient, evolutionarily conserved, and ubiquitous lipid signaling system found in all vertebrates, and which appears to have important regulatory functions throughout the human body (1). The endocannabinoid system has been implicated in a very broad number of physiological as well as pathophysiological processes including neural development, immune function, inflammation, appetite, metabolism and energy homeostasis, cardiovascular function, digestion, bone development and bone density, synaptic plasticity and learning, pain, reproduction, psychiatric disease, psychomotor behaviour, memory, wake/sleep cycles, and the regulation of stress and emotional state (2,3,4).

Components of the endocannabinoid system

The system consists of the cannabinoid 1 and 2 (CB_1 and CB_2) receptors, the CB receptor ligands N-arachidonoylethanolamine (i.e. "anandamide" or AEA) and 2-arachidonoylglycerol (2-AG) as well as the endocannabinoid-synthesizing and degrading enzymes fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL) **(Figure 1)** (2). Anandamide and 2-AG are considered the primary endogenous mediators of cannabinoid signaling, but other endogenous molecules which exert "cannabinoid-like" effects have also been described. These other molecules include 2-arachidonoylglycerol ether (noladin ether), N-arachidonoyl dopamine (NADA), virodhamine, N-homo-γ-linolenoylethanolamine (HEA) and N-docosatetraenoylethanolamine (DEA) (2,5,6,7,8). Molecules such as palmitoylethanolamide (PEA) and oleoylethanolamide (OEA) do not appear to bind to cannabinoid receptors but rather to a specific isozyme belonging to a class of nuclear receptors/transcription factors known as peroxisome proliferator-activated receptors (PPARs) (8). These endocannabinoids may, however, potentiate the effect of anandamide by competitive inhibition of FAAH, and/or through direct allosteric effects on other receptors such as the transient receptor potential vanilloid (TRPV1) channel (9). These types of effects have been generally referred to as the so-called "entourage effect" (9,10).

Endocannabinoid synthesis

Endocannabinoids are arachidonic acid derivatives which are synthesized "on demand" from membrane phospholipid precursors in response to cellular requirements (2,11,12,13). Anandamide is principally produced by the transfer of arachidonic acid from phosphatidylcholine to phosphatidylethanolamine by N-acyltransferase (NAT) to yield N-arachidonoylphosphatidylethanolamine (NAPE). NAPE is then hydrolyzed to form anandamide by a NAPE-specific phospholipase D (2,14). In contrast, 2-AG is principally synthesized through phospholipase C-β-mediated hydrolysis of phosphatidylinositol-4,5-bisphosphate, with arachidonic acid on the *sn-2* position, to yield diacylglycerol (DAG). DAG is then hydrolyzed to 2-AG by a DAG-lipase (2,14). While anandamide and 2-AG are both derivatives of arachidonic acid, they are synthesized by pathways distinct from those used to synthesize eicosanoids (15). Nevertheless, it appears that there may be a certain amount of cross-talk between the eicosanoid and endocannabinoid pathways (15).

Genetics and signaling through the cannabinoid receptors

Endocannabinoids such as anandamide and 2-AG, as well as the phytocannabinoids Δ^9-tetrahydrocannabinol (Δ^9-THC), Δ^8-THC, cannabinol and others, bind to and activate (with differing affinities and efficacies) the CB_1 and CB_2 receptors which are G-protein coupled receptors that activate G_i/G_o-dependent signaling cascades (16,17). The receptors are encoded by separate genes located on separate chromosomes; in humans, the CB_1 receptor gene (*CNR1*) locus is found on chromosome 5q15 whereas the CB_2 receptor gene (*CNR2*) locus is located on chromosome 1p36 (18). The *CNR1* coding sequence consists of one exon encoding a protein of 472 amino acids (19). The CB_1 receptor protein shares 97-99% amino acid sequence identity across species (human, rat, mouse) (19). As with the *CNR1* coding sequence, the *CNR2* coding sequence consists of only one exon, but it encodes a shorter protein 360 amino-acids in length (19). The human CB_2 receptor shares 48% amino acid identity with the human CB_1 receptor; the mouse CB_2 receptor shares 82% amino acid sequence identity with the human CB_2 receptor (19).

Activation of the CB_1 or CB_2 $G_{i/o}$-protein coupled receptors results in inhibition of adenylyl cyclase activity, decreased formation of cyclic AMP with a corresponding decrease in protein kinase A activity, and inhibition of Ca^{2+} influx through various Ca^{2+} channels; it also results in stimulation of inwardly rectifying potassium (K^+) channels and the mitogen-activated protein kinase signaling cascades (3,12). Anandamide is a partial agonist at CB receptors, and binds with slightly higher affinity at CB_1 compared to CB_2 receptors (2,20). 2-AG appears to bind equally well to both CB receptors (with slightly higher affinity to CB_1), but has greater potency and efficacy than anandamide at CB receptors (2,20).

In the central nervous system (CNS), the overall effect of CB_1 receptor activation is suppression of neurotransmitter release (5-hydroxytryptamine, glutamate, acetylcholine, GABA, noradrenaline, dopamine, D-aspartate, cholecystokinin) at both excitatory and inhibitory synapses with both short and long-term effects (2,16,21). Inhibition of neurotransmitter release occurs through a retrograde signaling mechanism whereby endocannabinoids synthesized and released from the post-synaptic neurons diffuse backwards across the synaptic cleft and bind to CB_1 receptors located on the pre-synaptic terminals (3). This retrograde signaling mechanism permits the regulation of neurotransmission in a precise spatio-temporal manner (3). In immune cells, activation of CB_2 receptors inhibits cytokine/chemokine release and neutrophil and macrophage migration, giving rise to complex modulatory effects on immune system function (17).

Cannabinoid receptor expression and receptor distribution

Most tissues contain a functional endocannabinoid system with the CB_1 and CB_2 receptors having distinct patterns of tissue expression. The CB_1 receptor is one of the most abundant G-protein coupled receptors in the central and peripheral nervous systems (17). It has been detected in the cerebral cortex, hippocampus, amygdala, basal ganglia, substantia nigra pars reticulata, internal and external segments of the globus pallidus and cerebellum (molecular layer), and at central and peripheral levels of the pain pathways including the periaqueductal gray matter, rostral ventrolateral medulla, the dorsal primary afferent spinal cord regions including the peripheral nociceptors, and the spinal interneurons (4,21,22). The CB_1 receptor is also expressed in many other organs and tissues including adipocytes, leukocytes, spleen, heart, lung, the gastrointestinal tract (liver, pancreas, stomach, and the small and large intestine), kidney, bladder, reproductive organs, skeletal muscle, bone, joints, and skin (23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41). CB_1 receptor expression appears to be relatively sparse in the brainstem region (4). CB_2 receptors are most highly concentrated in the tissues and cells of the immune system such as the leukocytes and the spleen, but can also be found in bone and to a lesser degree in liver and in nerve cells including astrocytes, oligodendrocytes and microglia, and even some neuronal sub-populations (reviewed in (42,43)).

Other molecular targets of cannabinoids

Besides the well-known CB_1 and CB_2 receptors, a number of different cannabinoids are believed to bind to a number of other molecular targets. Such targets include the third putative cannabinoid receptor GPR55, the transient receptor potential (TRP) cation channel family, and a class of nuclear receptors/transcription factors known as the peroxisome proliferator-activated receptors (PPARs). For additional details on this subject please consult the following resources (7,8,20,44). Modulation of these other cannabinoid targets adds additional layers of complexity to the known myriad effects of cannabinoids.

Signal termination

Endocannabinoid signaling is rapidly terminated by the action of two hydrolytic enzymes: fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL) (3). FAAH is primarily localized post-synaptically (45,46) and preferentially degrades anandamide (13); MAGL is primarily localized pre-synaptically (45,46) and favors the catabolism of 2-AG (13).

Dysregulation of the endocannabinoid system and general therapeutic challenges of using cannabinoids

Dysregulation of the endocannabinoid system appears to be connected to a number of pathological conditions, with the changes in the functioning of the system being either protective or maladaptive (47). Modulation of the endocannabinoid system either through the targeted inhibition of specific metabolic pathways, and/or directed agonism or antagonism of its receptors may hold therapeutic promise (12). However, a major and consistent therapeutic challenge confronting the routine use of psychoactive cannabinoids (e.g. THC) in the clinic has remained that of achieving selective targeting of the site of disease and the sparing of other bodily regions such as the mood and cognitive centres of the brain (21,47,48,49,50).

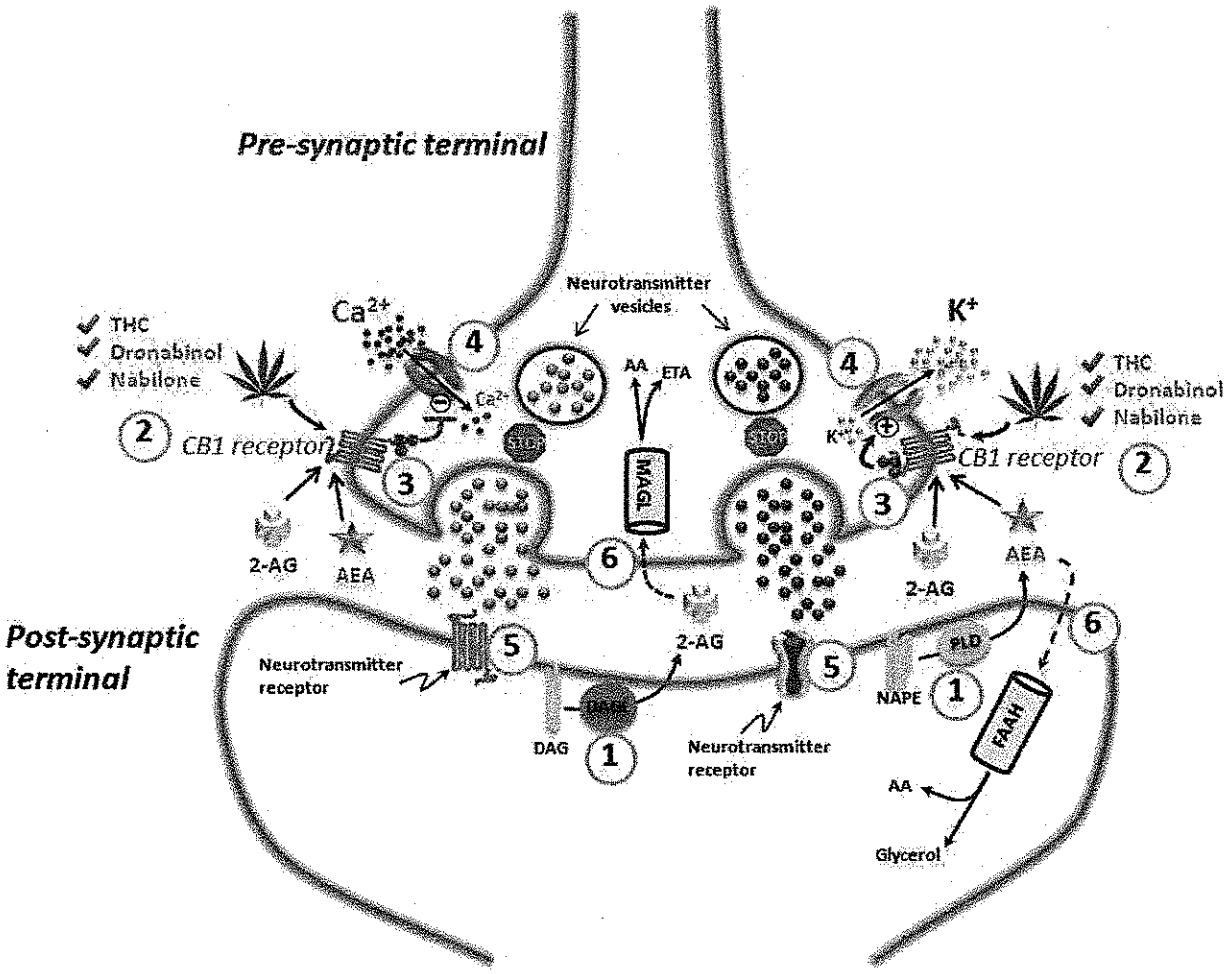

Figure 1. The Endocannabinoid System in the Nervous System

(1) Endocannabinoids are manufactured "on-demand" in the post-synaptic terminals: anandamide (AEA) is generated from phospholipase-D (PLD)-mediated hydrolysis of the membrane lipid N-arachidonoylphosphatidylethanolamine (NAPE); 2-AG from the diacylglycerol lipase (DAGL)-mediated hydrolysis of the membrane lipid diacylglycerol (DAG); **(2)** These endocannabinoids (AEA and 2-AG) diffuse retrogradely towards the pre-synaptic terminals and like exogenous cannabinoids such as THC (from cannabis), dronabinol, and nabilone, they bind and activate the pre-synaptic G-protein-coupled CB_1 receptors; **(3)** Binding of phytocannabinoids and endocannabinoids to the CB_1 receptors triggers the activation and release of the G_i/G_o proteins from the CB receptors and inhibits adenylyl cyclase, thus decreasing the formation of cyclic AMP and the activity of protein kinase A; **(4)** Release of the G_i/G_o proteins also results in the opening of inwardly-rectifying K^+ channels (depicted with a "+") causing a hyperpolarization of the pre-synaptic terminals, and the closing of Ca^{2+} channels (depicted with a "-"), arresting the release of stored excitatory and inhibitory neurotransmitters (e.g. glutamate, GABA, 5-hydroxytryptamine (5-HT), acetylcholine, noradrenaline, dopamine, D-aspartate and cholecystokinin) which **(5)** once released, diffuse and bind to post-synaptic receptors; **(6)** Anandamide and 2-AG re-enter the post- or pre-synaptic nerve terminals (possibly through the actions of a specialized transporter depicted by a "dashed" line) where they are respectively catabolized by fatty acid amide hydrolase (FAAH) or monoacylglycerol lipase (MAGL) to yield either arachidonic acid (AA) and ethanolamine (ETA), or arachidonic acid and glycerol. See text for additional details. Figure adapted from (51,52,53).

1.1 Cannabis

1.1.1 Chemistry and composition

Marihuana (Marijuana) is the common name for *Cannabis sativa* (i.e. cannabis), a hemp plant that grows throughout temperate and tropical climates (54). The leaves and flowering tops of *Cannabis* plants contain at least 489 distinct compounds distributed among 18 different chemical classes, and harbor more than 70 different phytocannabinoids (55). The principal cannabinoids appear to be delta-9-tetrahydrocannabinol (i.e. Δ^9-THC, THC), cannabinol (CBN), and cannabidiol (CBD) (56,57,58), although the relative abundance of these and other cannabinoids can vary depending on a number of factors such as the *Cannabis* strain, the soil and climate conditions, and the cultivation techniques (59,60). Other cannabinoids found in cannabis include cannabigerol (CBG), cannabichromene (CBC), tetrahydrocannabivarin (THCV) and many others (55). In the living plant, these phytocannabinoids exist as both inactive monocarboxylic acids (e.g. THCA) and as active decarboxylated forms (e.g. THC); however, heating (at temperatures above 120 °C) promotes decarboxylation (e.g. THCA to THC) and results in biological activation (61,62,63). Furthermore, pyrolysis transforms each of the hundreds of compounds in cannabis into a number of other compounds, many of which remain to be characterized both chemically and pharmacologically. Therefore, marihuana (cannabis) can be considered a very crude drug containing a very large number of chemical and pharmacological constituents, the properties of which are only slowly being understood.

Among all the chemical constituents of cannabis, and particularly among the cannabinoids, Δ^9-THC is by far the best studied and is responsible for many, if not most, of the physical and psychotropic effects of cannabis (64). Other cannabinoids (such as CBD, CBC, CBG) are present in lesser amounts in the plant and have little, if any, psychotropic properties (64). It is reasonable to consider about 10% (range 1 - 30%) as an average for Δ^9-THC content in cannabis found on the illicit market in Canada (internal communication). The dried marihuana currently provided by Health Canada is composed of the mature flowering heads of female plants and contains 12.5 ±2% total THC (Δ^9-THC and Δ^9-THCA), and less than 0.5% CBD, CBG, CBN, and CBC (65). The MS-17/338 production line has THC concentrations typically higher than 10%, with the mature flowering heads containing the highest concentration of THC (65). The plant is cultivated and harvested in compliance with Good Manufacturing Practices, by Prairie Plant Systems Inc. under contract to Health Canada (66). Furthermore, the product is irradiated to ensure that users whose immune systems may be compromised are not exposed to toxic spores which may contaminate the plant material, and the finished product lot release is based on the results of bacterial, fungal, and moisture testing (65). Irradiated pouches containing the dried cannabis are kept sterile over long-term cold storage, with measures of viable microbes being below detection (Health Canada internal communication).

1.1.2 Other constituents

The large number of compounds found in cannabis span many chemical classes including cannabinoids, nitrogenous compounds, amino acids, proteins, enzymes, glycoproteins, hydrocarbons, simple alcohols, aldehydes, ketones and acids, fatty acids, simple esters and lactones, steroids, terpenes, non-cannabinoid phenols, flavonoids, vitamins, and pigments (55). Furthermore, differences in the presence and the relative abundance of some of these various components have been investigated, and differences have been noted between cannabis extract, vapour, and smoke, and also between cannabis varieties (67). Of note, cannabis smoke contains many compounds not observed in either extracts or vapour, including a number which are known or suspected carcinogens or mutagens (67,68,69). Moreover, comparisons between cannabis smoke and tobacco smoke have shown that the former contains many of the same carcinogenic chemicals found in tobacco smoke (68,70).

Relatively little is known about the pharmacological actions of the various other compounds found within cannabis (e.g. terpenes, flavonoids). However, it is believed that some of these compounds (e.g. terpenes) may have a broad spectrum of action (e.g. anti-oxidant, anti-anxiety, anti-inflammatory, anti-bacterial, anti-neoplastic, anti-malarial), but this information comes from a few *in vitro* and *in vivo* studies and no clinical trials exist to support these claims. Terpenes vary widely among cannabis varieties and are thought to be primarily responsible for differences in fragrance among the different *Cannabis* strains (59). Furthermore, it is thought that terpenes may contribute to the distinctive smoking qualities and possibly to the character of the "high" associated with smoking cannabis (59), but again, this has not been studied in any detail. The concept that terpenes may somehow modify or enhance the physiological effects of the cannabinoids (71,72) is, for the moment, hypothetical as there is little, if any, pre-clinical evidence to support this hypothesis and no clinical trials on this subject have been carried out to date.

1.1.3 Stability and storage

Most of the information on the stability of marihuana/cannabis does not distinguish between Δ^9-THC and its carboxylic acid (Δ^9-THCA). The latter is transformed to Δ^9-THC by heating during vapourization or cooking, or by pyrolysis during smoking or in the inlet of gas chromatographs used in forensic analysis (73). Heat, light, humidity, acidity and oxidation all affect the stability of cannabis and cannabinoids (74,75). 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 (76). Even when stored at +18 °C, only a third of the THC content is lost over a five-year period with some increase in the concentration of CBN. Lower-potency cigarettes (1.15% THC) appear to lose more THC compared to higher potency cigarettes (2.87% THC) (76). Stability data for cannabis distributed by Health Canada indicate that, when stored in the refrigerator (4 °C ±1 °C) or freezer (-17 °C to -20 °C ±1°C), the finished product is stable for over 2 years without significant conversion of Δ^9-THCA to Δ^9-THC or any alterations in colour or aroma (Health Canada internal communication). The moisture content of the sealed, finished product is constant at 11 - 12% over a period of 12 months. When stored at room temperature (20 °C ± 2 °C), alterations in colour and aroma are detected in the finished product at 9 months, and conversion of Δ^9-THCA to Δ^9-THC is detected as early as 1.5 months, and increases to nearly 25% at 18 months (Health Canada internal communication). The ideal storage temperature for the finished dried cannabis product is 2 °C to 6 °C with a shelf-life of 12 months (Health Canada internal communication).

2.0 Clinical Pharmacology

2.1 Pharmacodynamics

Much of the pharmacodynamic information on cannabis refers to the effects of the major constituent Δ^9-THC which acts as a partial agonist at both CB receptors (77), has activity at non-CB receptors and other targets (78), and is responsible for the psychoactive effects of cannabis through its actions at the CB_1 receptor (79). Δ^8-THC (an isomer of Δ^9-THC) is found in smaller amounts in the plant (64), but like Δ^9-THC, it is a partial agonist at both CB receptors and shares relatively similar efficacy and potency with Δ^9-THC in *in vitro* assays (77). An *in vivo* animal study and one clinical study suggest Δ^8-THC to be a more potent anti-emetic than Δ^9-THC (80,81).

Cannabinol (CBN) is a product of Δ^9-THC oxidation and has 10% of the activity of Δ^9-THC (82). Its effects are not well studied but it appeared to have some possible immunosuppressive properties in a small number of *in vitro* studies (83). Cannabigerol (CBG) is a partial $CB_{1/2}$ receptor agonist and a small number of *in vitro* studies suggest it may have some anti-inflammatory and analgesic properties (44,82,84,85). It may also block 5-HT_{1A} receptors and act as an α_2-adrenoceptor agonist (86).

Cannabidiol (CBD) lacks detectable psychoactivity and does not appear to bind to either CB_1 or CB_2 receptors at physiologically meaningful concentrations, but it affects the activity of a significant number of other targets including ion channels, receptors, and enzymes (reviewed in (16,82,87)). Results from pre-clinical studies suggest CBD has anti-inflammatory, analgesic, anti-nausea, anti-emetic, anti-psychotic, anti-ischemic, anxiolytic, and anti-epileptiform effects (reviewed in (82,88)).

Tetrahydrocannabivarin (THCV) acts as a CB_1 receptor antagonist and CB_2 receptor partial agonist *in vitro* and *in vivo* (89,90), and pre-clinical studies suggest it may have anti-epileptiform/anti-convulsant properties (91).

Much of what is known about the beneficial properties of the non-psychotropic cannabinoids (e.g. CBD, THCV) is 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, liver disease, osteogenesis, and cancer (reviewed in (16,82,92)). For more in-depth information on the pharmacology of cannabinoids, the reader is invited to consult the following resources (20,82,93).

Phytocannabinoid-Phytocannabinoid Interaction and Phytocannabinoid Differences among Cannabis Strains

Despite anecdotal claims, there is limited reliable information regarding real or potential interactions, of biological or physiological significance, among phytocannabinoids, especially Δ^9-THC and CBD. The limited information that exists is complex and requires further clarification through additional investigation. The following paragraphs summarize the available information on this subject.

Factors affecting the nature of the potential phytocannabinoid-phytocannabinoid interactions

Various studies have reported either potentiating, opposing, or neutral interactions between Δ^9-THC and CBD (94,95,96,97,98,99,100,101,102,103,104,105,106,107,108,109). The discrepancies in the nature of the interactions between Δ^9-THC and CBD reported in the literature may be explained by differences in the doses and ratios of THC and CBD used in the different studies, differences in the routes of administration, dose ordering effects (CBD pre-treatment vs. simultaneous co-administration), differences in the duration or chronicity of treatment (acute vs. chronic), differences in the animal species used, as well as the particular biological or physiological end-points being measured (110).

Pharmacokinetic vs. pharmacodynamic interactions

In general, there appear to be two types of mechanisms which could govern possible interactions between CBD and Δ^9-THC: those of a *pharmacokinetic* origin (102,110), and those of a *pharmacodynamic* origin (95,97). Despite the limited and complex nature of the available information, it generally appears that pre-administration of CBD may potentiate some of the effects of THC (through a pharmacokinetic mechanism), whereas simultaneous co-administration of CBD and THC may result in the attenuation of some of the effects of THC (through a pharmacodynamic mechanism). Furthermore, the ratio between the two phytocannabinoids also appears to play a role in determining whether the overall effect will be of a potentiating or antagonistic nature. CBD-mediated attenuation of THC-induced effects may be observed when the ratio of CBD to THC is at least 8 : 1 (±11.1) (96,109), whereas CBD appears to potentiate some of the effects associated with THC when the CBD to THC ratio is around 2 : 1 (±1.4) (109). Potentiation of THC effects by CBD may be caused by inhibition of THC metabolism in the liver, resulting in higher plasma levels of THC (102,110). There is virtually no information in the peer-reviewed scientific or medical literature concerning the effects of varying CBD to THC ratios in the treatment of different medical disorders.

Psychological and physiological effects associated with varying phytocannabinoid concentrations

There are only a handful of studies examining the neurophysiological, cognitive, subjective, or behavioural effects of varying the concentrations of Δ^9-THC, CBD, or other cannabinoids such as cannabichromene (CBC) in smoked cannabis (101,111). In one study, 24 healthy men and women who had reported using cannabis at least 10 times in their lifetime were subjected to a double-blind, placebo-controlled, mixed between- and within-subject clinical trial that showed that deliberate systematic variations in the levels of either CBD or CBC in smoked cannabis were not associated with any significant differences in any of the measured subjective, physiological, or performance tests (101). In another study, the subjective effects associated with the smoked or oral administration of cannabis plant material were directly compared to those associated with smoked or oral administration of Δ^9-THC (using matched doses of Δ^9-THC) to normal, healthy subjects (111). This double-blind, placebo-controlled, within-subject, crossover clinical study reported few reliable differences between the THC-only and whole-plant cannabis conditions (111). The authors further concluded that other cannabinoids present in the cannabis plant material did not alter the subjective effects of cannabis, but they speculated that cannabis samples with higher levels of cannabinoids or different ratios of the individual cannabinoids could conceivably produce different results, although no evidence to support this claim was provided in the study. They also hypothesized that whole-plant cannabis and THC alone could differ on other outcome measures more relevant to clinical entities (e.g. spasticity or neuropathic pain). With the possible exception of one study (112), (see section 4.6.2.3. Cancer Pain), which suggested differences between a whole-plant cannabis extract (i.e. nabiximols, marketed as Sativex®) and THC alone on cancer pain analgesia, no other clinical studies have examined this possibility. One study compared the subjective and physiological effects of oral THC to those of nabiximols in normal, healthy subjects (107). The authors reported the absence of any modulatory effect of CBD (or other components of cannabis) at low therapeutic cannabinoid doses, with the potential exception of the subjective "high" (107). An internet-based, cross-sectional study of 1 877 individuals with a consistent history of cannabis use reported that those individuals who had indicated using cannabis with a higher CBD to THC ratio had also reported experiencing fewer psychotic experiences (an effect typically associated with exposure to higher doses of THC) (113). However, the authors noted that the effects were subtle. The study was also hampered by a number of important methodological issues suggesting that the conclusions should be interpreted with caution. In summary, further careful study is required to elucidate the influence of CBD, and other phytocannabinoids or terpenoids, on the physiological or psychological effects associated with the use of Δ^9-THC, as well as on any medical disorders. There is presently insufficient scientific and clinical evidence to lend support to the anecdotal claims that one strain of cannabis may be more beneficial than another one for a particular medical condition.

Table 1 (next page), adapted from a review (114), 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 (115,116,117). Effects differ greatly among individuals and may be greater in those who are severely ill, elderly, or those taking other drugs.

Most of the available information regarding the acute effects of smoking cannabis comes from studies conducted on recreational users, with much less information available from clinical studies of patients using cannabis for medical purposes. The acute effects of smoking or eating cannabis include euphoria (the marihuana "high") as well as cardiovascular, bronchopulmonary, ocular, psychological and psychomotor effects. Maximum euphoria typically occurs within 15 min after smoking and generally takes longer with oral administration (64). However, some people can experience dysphoria and anxiety (118). 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 acute physiological effects associated with the consumption of cannabis (117,119,120,121) .

The short-term psychoactive effects associated with cannabis smoking in recreational users include the above-mentioned euphoria but also 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 (122). This is followed by a depressant period (123). While there is some inconsistency in reports regarding the acute effects of cannabis on memory and motor skills (124,125,126), most reviews note that cannabis use is associated with impaired function on a variety of cognitive and short-term memory tasks (83,123,127,128,129,130). The levels of Δ^9-THC in the plasma after smoking appear to have a dose, time, and concentration-dependent effect on cognitive function (131,132,133). Driving and operation of intricate machinery, including aircraft, may be significantly impaired (134,135,136,137).

Table 1: Pharmacologic Actions of Cannabis (adapted from (114) with additional references)

Body System/Effect	Detail of Effects
Central Nervous System (CNS)	
Psychological	Euphoria ("high"), dysphoria, anxiety, depersonalization, precipitation or aggravation of psychosis (64,117,118,138,139,140,141,142,143,144,145,146,147,148,149,150,151,152,153,154,155,156,157,158).
Perception	Heightened sensory perception, distortion of space and time sense, hallucinations, misperceptions (151,156,159,160,161,162,163).
Sedative	Generalised CNS depression, drowsiness, somnolence; additive with other CNS depressants (opioids/alcohol) (117,142,157,158,164,165,166,167,168,169,170,171,172,173,174) .
Cognition, psychomotor performance	Fragmentation of thoughts, mental clouding, memory impairment, global impairment of performance especially in complex and demanding tasks (101,129,134,135,136,137,157,174,175,176,177,178,179,180,181).
Motor function	Incoordination, ataxia, dysarthria, weakness (117,162,168,174,182,183) .
Analgesic	Modest effect for chronic non-cancer pain (142,157,158,164,165,168,172,173,184,185,186,187,188,189).
Anti-nausea/anti-emetic; hyper-emetic	Observed with acute doses (88,190,191,192)-- Tolerance may occur with chronic use (193). Hyperemesis may be observed with larger doses or chronic use (194,195,196,197,198,199,200,201,202,203,204).
Appetite	Increased in normal, healthy subjects, but also in patients suffering from HIV/AIDS-associated anorexia/cachexia (166,167,174,205,206,207,208,209).
Tolerance	To most behavioural and somatic effects, including the "high" (with chronic use) (210,211,212,213,214,215,216,217,218) and (see section 2.4).
Dependence, withdrawal syndrome	Dependence has been produced experimentally, and observed clinically, following prolonged intoxication ((122,156,210,219,220,221) and see section 2.4). Abstinence leads to withdrawal symptoms which can include anger, anxiety, restlessness, irritability, depressed mood, disturbed sleep, strange dreams, decreased appetite, and weight loss ((156,210,222) and also see section 2.4).
Cardiovascular and Cerebrovascular System	
Heart rate/rhythm	Tachycardia with acute dosage; tolerance developing with chronic exposure (117,119,120,121,157,158,223,224,225,226). Premature ventricular contractions, atrial fibrillation, ventricular arrhythmia also seen with acute doses (121,174,227,228,229,230,231).
Peripheral circulation	Vasodilatation, conjunctival redness, supine hypertension, postural hypotension (170,174,225,227,232,233,234).
Cardiac output	Increased cardiac output (227) and myocardial oxygen demand (232).
Cerebral blood flow	Increased with acute dose, decreased with chronic use, region-dependent variations (225,235).
Myocardial infarction	Increased risk of acute myocardial infarction within 1 h after smoking cannabis especially in individuals with existing cardiovascular disease (121,232).
Stroke	Increased risk of experiencing stroke after an acute episode of smoking cannabis (227,236,237).
Respiratory System	
Carcinogenesis/mutagenesis	Cannabis smoke contains many of the same chemicals as tobacco smoke, and cannabis smoke condensates are more cytotoxic and mutagenic than condensates from tobacco smoke (68,70). Conflicting evidence linking cannabis smoking and cancer (238,239,240,241).
Histopathologic changes/ inflammation	Chronic cannabis smoking associated with histopathologic changes in the lung (basal cell hyperplasia, stratification, goblet cell hyperplasia, cell disorganization, inflammation, basement membrane thickening, and squamous cell metaplasia) (242). Long-term smoking associated with

Body System/Effect	Detail of Effects
	cough, increased production of phlegm, and wheeze (243).
Bronchodilatation	Acute exposure causes dilatation; possibly reversed with chronic exposure (by smoking) (243).
Pulmonary function (FEV_1; FVC)	Acute, low-level exposure possibly stimulatory; long-term, heavy smoking possibly associated with increased obstruction and decreased lung function (243,244,245,246,247).
Gastrointestinal System	
General pharmacologic actions	Decreased gastrointestinal motility, decreased secretion, decreased gastric/colonic emptying, anti-inflammatory actions (31,157,189,248).
Liver	Increased risk of hepatic steatosis/fibrosis, especially in patients with Hepatitis C (33,249,250,251). Increased Hepatitis C treatment adherence resulting in a potential sustained absence of detectable levels of Hepatitis C virus (252).
Pancreas	Acute risk of pancreatitis with chronic, heavy, daily use (253,254,255,256).
Musculoskeletal system	
General pharmacologic actions	Possible beneficial effect in chronic pain from rheumatoid arthritis (257,258,259) and fibromyalgia (158,260,261). May attenuate spasticity from multiple sclerosis (164,165,188,262). May negatively impact bone healing (263).
Eye	
General pharmacologic actions	Decreased intra-ocular pressure (264,265).
Immune System	
General pharmacologic actions	Complex immunomodulatory effects with suppressive and/or stimulatory effects (acute and chronic dosing) (24,266).
Reproductive System	
Males	With chronic administration: anti-androgenic, decreased sperm count and sperm motility, altered sperm morphology in animals (and possibly in humans) (267,268). Tolerance to these effects may develop. Possible inhibitory effects on sexual behaviour in men (269).
Females	Effects inconclusive in women (possibly due to tolerance) but changes in menstrual cycle, suppression of ovulation, and complex effects on prolactin secretion observed in female animals (268,270,271). Dose-dependent stimulatory or inhibitory effects on sexual behaviour in women (269).

2.2 Pharmacokinetics

This section is restricted to human pharmacokinetics of smoked and vapourized cannabis, oral preparations including prescription cannabinoid medicines such as dronabinol (Marinol®) and nabiximols (Sativex®), and other routes of administration (e.g. rectal, topical).

2.2.1 Absorption

2.2.1.1 Smoked cannabis

Smoking cannabis results in more rapid onset of action (within minutes), higher blood levels of cannabinoids, and a shorter duration of pharmacodynamic effects compared to oral administration (62). The amount of Δ^9-THC delivered from cannabis cigarettes is not uniform and is a major variable in the assessment of absorption (62). 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 (62,272). While it has been reported that smokers can titrate their Δ^9-THC intake by adapting their smoking behaviour to obtain desired levels of Δ^9-THC (273), other reasons may also explain the observed variation in smoking topography (274). Δ^9-THC absorption by inhalation is extremely rapid but quite variable, with a bioavailability of 2 - 56% through the smoking route depending on depth of inhalation, puff duration, and breathhold (275,276). In practice, a maximum of 25 - 27% of the THC content in a cannabis cigarette is absorbed or delivered to the systemic circulation from the total available amount (117,277).

Standardized cannabis cigarettes have been developed by the National Institute on Drug Abuse (NIDA), and the relationships among cannabis Δ^9-THC content, dose administered, and resultant plasma levels have been investigated. Mean plasma Δ^9-THC concentrations were 7.0 ±8.1 ng/mL and 18.1 ±12.0 ng/mL upon a single inhalation of either a 1.75% "low-dose" Δ^9-THC cannabis cigarette (total available dose ~16 mg Δ^9-THC), or a 3.55% Δ^9-THC "high-dose" cannabis cigarette (total available dose ~34 mg Δ^9-THC) (62). Smoking cannabis containing 1.64% Δ^9-THC (mean available dose 13.0 mg Δ^9-THC) resulted in mean peak THC plasma levels of 77 ng/mL (278). Similarly, smoking cannabis joints containing 1.8% Δ^9-THC (total available dose ~14 mg Δ^9-THC) resulted in mean peak plasma THC levels of approximately 75 ng/mL, whereas with 3.6% Δ^9-THC (total available dose ~28.8 mg Δ^9-THC), mean peak plasma Δ^9-THC levels of 100 ng/mL were attained (279). Smoking a 25 mg dose of cannabis containing 2.5, 6, or 9.4% Δ^9-THC (total available doses of ~0.6, 1.5, or 2.4 mg Δ^9-THC) was associated with mean peak plasma Δ^9-THC concentrations of 10, 25, or 45 ng/mL Δ^9-THC, respectively (172). Smoking one cannabis cigarette (mean weight 0.79 ±0.16 g) containing 6.8% ±0.2 THC, 0.25% ±0.08 CBD, and 0.21% ±0.02 CBN (w/w) yielding a total THC, CBD, and CBN content of 54, 2.0, and 1.7 mg of these cannabinoids per cigarette, respectively, was associated with a median whole blood THC concentration of approximately 60 ng/mL Δ^9-THC (range 13 - 63 ng/mL) (280).

2.2.1.2 Vapourized cannabis

Vapourization of cannabis has been explored as an alternative to smoking. The potential advantages of vapourization 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 Δ^9-THC from the cannabis material (273,281,282,283,284). The subjective effects and plasma concentrations of Δ^9-THC obtained by vapourization of cannabis are comparable to those obtained by smoking cannabis, with absorption being somewhat faster with the vapourizer compared to smoking, according to one study (273). In addition, the study reported that the vapourizer was well tolerated with no reported adverse effects, and was preferred over smoking by the test subjects (273). While vapourization has been reported to be amenable to self-titration (as has been claimed for smoking) (273,283), the proper use of the vapourizer for optimal administration of cannabis for therapeutic purposes needs to be established in more detail (284). The amount and type of cannabis placed in the vapourizer, the vapourizing temperature and duration of vapourization, and the balloon volume are some of the parameters that can affect the delivery of Δ^9-THC (283). Bioequivalence of vapourization compared to smoking has not been thoroughly established. Inhalation of vapourized cannabis (0.9 g of 3.56% Δ^9-THC; total available dose of 32 mg of Δ^9-THC) in a group of patients taking stable doses of sustained-release morphine or oxycodone resulted in mean plasma Δ^9-THC levels of 126.1 ng/mL within 3 min after starting cannabis inhalation, rapidly declining to 33.7 ng/mL Δ^9-THC at 10 min, and reaching 6.4 ng/mL Δ^9-THC at 60 min (187). Peak Δ^9-THC concentration was achieved at 3 min in all study participants (187). Maximal subjective "high" ratings occurred at 60 min following beginning of

inhalation, with a stronger and more sustained subjective "high" score for individuals taking oxycodone compared to those taking morphine (187). No statistically significant changes were reported for the AUC_{12} for either morphine or oxycodone, but there appeared to be a statistically significant decrease in the maximum concentration (C_{max}) of morphine sulfate, and a delay in the time needed to reach C_{max} for morphine during cannabis exposure (187).

2.2.1.3 Oral

Whereas the central nervous system and physiological effects occur within minutes by the smoking route or by vapourization (129,285), these effects proceed on a time scale of hours in the case of oral ingestion (285,286). Oral administration results in a slower onset of action, lower peak blood levels of cannabinoids, and a longer duration of pharmacodynamic effects compared to smoking (62). The psychotropic effect or "high" occurs much more quickly by the smoking than by the oral route, which is the reason why smoking appears to be the preferred route of administration by many, especially recreational users (287).

For orally administered prescription cannabinoid medicines such as synthetic Δ^9-THC (dronabinol, marketed as Marinol®), only 10 - 20% of the administered dose enters the systemic circulation indicating extensive first-pass metabolism (174). Administration of a single 2.5 mg dose of dronabinol in healthy volunteers was associated with a mean plasma Δ^9-THC C_{max} of 0.7 ng/mL (range: 0.3 - 1 ng/mL), and a mean time to peak plasma Δ^9-THC concentration of 2 h (range: 30 min - 4 h) (174). A single 5 mg dose of dronabinol gave a reported mean plasma Δ^9-THC C_{max} of 1.8 ng/mL (range: 0.4 - 3.3 ng/mL), whereas a single 10 mg dose yielded a mean plasma Δ^9-THC C_{max} of 6.2 ng/mL (range: 3.5 - 9 ng/mL) (174). Again, the mean time to peak plasma Δ^9-THC concentration ranged from 30 min - 3 h. Twice daily dosing of dronabinol (individual doses of 2.5 mg, 5 mg, 10 mg, b.i.d.) in healthy volunteers yielded plasma Δ^9-THC C_{max} values of 1.3 ng/mL (range: 0.7 - 1.9 ng/mL), 2.9 ng/mL (range: 1.2 - 4.7 ng/mL), and 7.9 ng/mL (range: 3.3 - 12.4 ng/mL), respectively, with a time to peak plasma Δ^9-THC concentration ranging between 30 min and 4 h after oral administration (174). Continuous dosing for seven days with 20 mg doses of dronabinol (total daily doses of 40 -120 mg dronabinol) gave mean plasma Δ^9-THC concentrations of ~20 ng/mL (288).

Δ^9-THC can also be absorbed orally by ingestion of foods containing cannabis (e.g. butters, oils, brownies, cookies), and teas prepared from leaves and flowering tops. Absorption from an oral dose of 20 mg Δ^9-THC in a chocolate cookie was described as slow and unreliable (272), with a systemic availability of only 4 - 12% (278). While most subjects displayed peak plasma Δ^9-THC concentrations (6 ng/mL) between 1 - 2 h after ingestion, some of the 11 subjects in the study only peaked at 6 h, and many had more than one peak (62). Consumption of cannabis-laced brownies containing 2.8% Δ^9-THC (44.8 mg total Δ^9-THC) was associated with changes in behaviour, although the effects were slow to appear and variable (286). Peak effects occurred 2.5 - 3.5 h after dosing. Modest changes in pulse and blood pressure were also noted. Plasma concentrations of Δ^9-THC were not measured in this study. In another study, ingestion of brownies containing a low dose of Δ^9-THC (9 mg THC/brownie) was associated with mean peak plasma Δ^9-THC levels of 5 ng/mL Δ^9-THC (111). Ingestion of brownies containing a high dose of Δ^9-THC (~13 mg Δ^9-THC/brownie) was associated with mean peak plasma Δ^9-THC levels of 6 or 9 ng/mL Δ^9-THC depending on whether the THC in the brownie came from plant material or was added as pure THC (111). Using equivalent amounts of Δ^9-THC, inhalation by smoking cannabis yielded peak plasma levels of Δ^9-THC several-fold (five to six times or more) higher than when Δ^9-THC was absorbed through the oral route (111). Tea made from dried cannabis flowering tops (19.1% Δ^9-THCA (tetrahydrocannabinolic acid), 0.6% Δ^9-THC) has been documented, but the bioavailability of Δ^9-THC from such teas is likely to be smaller than that achieved by smoking because of the poor water solubility of Δ^9-THC and the hepatic first-pass effect (289).

2.2.1.4 Oro-mucosal

Following a single oro-mucosal administration of nabiximols (Sativex®) (four sprays totalling 10.8 mg Δ^9-THC and 10 mg CBD), mean peak plasma concentrations of both THC (~5.5 ng/mL) and CBD (~3 ng/mL) typically occur within 2 - 4 h, although there is wide inter-individual variation in the peak cannabinoid plasma concentrations and in the time to onset and peak of effects (290). When administered oro-mucosally, blood levels of Δ^9-THC and other cannabinoids are lower than those achieved by inhalation of the same dose of smoked cannabis, but Δ^9-THC blood levels were comparable to those seen with oral administration of dronabinol (108,290). Oro-mucosal administration of nabiximols is amenable to self-titration (107,259,291,292).

2.2.1.5 Rectal

While Δ^9-THC itself is not absorbed through the rectal route, the pro-drug Δ^9-THC-hemisuccinate is absorbed; this fact, combined with decreased first-pass metabolism through the rectal route, results in a higher bioavailability of Δ^9-THC by the rectal route (52 - 61%) than by the oral route (293,294,295,296,297). Plasma concentrations of Δ^9-THC are dose and vehicle-dependent, and also vary according to the chemical structure of the THC ester (296). In humans, rectal doses of 2.5 - 5.0 mg of the hemisuccinate ester of Δ^9-THC were associated with peak plasma levels of Δ^9-THC ranging between 1.1 and 4.1 ng/mL within 2 - 8 h, and peak plasma levels of carboxy-Δ^9-THC ranging between 6.1 - 42.0 ng/mL within 1 - 8 h after administration (293).

2.2.1.6 Topical

Cannabinoids are highly hydrophobic, making transport across the aqueous layer of the skin the rate-limiting step in the diffusion process (62). No clinical studies exist regarding the percutaneous absorption of cannabis-containing ointments, creams, or lotions. However, some research has been carried out on transdermal delivery of synthetic and natural cannabinoids using a dermal patch (298,299). A patch containing 8 mg of Δ^8-THC yielded a mean steady-state plasma concentration of 4.4 ng/mL Δ^8-THC within 1.4 h in a guinea pig model, and this concentration was maintained for at least 48 h (298). Permeation of cannabidiol (CBD) and cannabinol (CBN) was found to be 10-fold higher than for Δ^8-THC (300).

2.2.2 Distribution

Distribution of Δ^9-THC is time-dependent and begins immediately after absorption. It is taken up primarily by fatty tissues and highly perfused organs such as the brain, heart, lung, and liver (62). Δ^9-THC has a large apparent volume of distribution, approximately 10 L/kg, because of its high lipid solubility (301). The plasma protein binding of Δ^9-THC and its metabolites is approximately 97% (302,303). Δ^9-THC is mainly bound to low-density lipoproteins, with up to 10% present in red blood cells (304), while the metabolite, 11-hydroxy THC is strongly bound to albumin with only 1% found in the free-fraction (305).

The highest concentrations of Δ^9-THC are found in the heart and in adipose tissue, with levels reaching 10 and 1000 times that of plasma, respectively (306). Despite the high perfusion level of the brain, the blood-brain barrier (BBB) appears to limit the access and accumulation of Δ^9-THC in this organ (62,307,308), and the delay in correlating peak plasma concentration to psychoactive effects may be attributed to the time required for Δ^9-THC to traverse this barrier (272).

Δ^9-THC accumulates and is retained in fatty tissue, and its release from this storage site into the blood is slow (307). It is not certain if Δ^9-THC persists in the brain in the long-term; however, the presence of residual cognitive deficits in abstinent heavy cannabis users raises the possibility that Δ^9-THC may be retained in the brain at least in the short-term (179,309). One animal study suggested food deprivation or adrenocorticotropic hormone (ACTH) administration in rats accelerates lipolysis and the release of Δ^9-THC from fat stores, however further research is needed to determine if these effects are associated with intoxication or behavioural/cognitive changes (310).

2.2.3 Metabolism

Most cannabinoid metabolism occurs in the liver, and different metabolites predominate depending on the route of administration (62,272). The complex metabolism of Δ^9-THC involves allylic oxidation, epoxidation, decarboxylation, and conjugation (272). Δ^9-THC is oxidized by the xenobiotic-metabolizing cytochrome P450 (CYP) mixed-function oxidases 2C9, 2C19, and 3A4 (62). The major initial metabolites of Δ^9-THC are the active 11-hydroxy Δ^9-THC, and the non-active 11-nor-9-carboxy Δ^9-THC (62). 11-hydroxy Δ^9-THC is rapidly formed by the action of the above-mentioned hepatic microsomal oxidases, and plasma levels of this metabolite parallel the duration of observable drug action (311,312).

As would be expected, oral administration of Δ^9-THC results in a greater metabolism of Δ^9-THC to the 11-hydroxy metabolite compared to administration by smoking (or vapourization), resulting in similar plasma concentrations of Δ^9-THC and 11-hydroxy Δ^9-THC through the oral route vs. inhalation (276). Information from the dronabinol (Marinol®) product monograph suggests that single doses of 2.5 mg, 5 mg, and 10 mg of Δ^9-THC in healthy volunteers result in mean plasma C_{max} values of 11-hydroxy Δ^9-THC of 1.19 ng/mL (range: 0.4 - 1.9 ng/mL), 2.23 ng/mL (range: 0.7 - 3.7 ng/mL), and 7.51 ng/mL (range: 2.25 - 12.8 ng/mL), respectively (174).

Twice daily dosing of dronabinol (individual doses of 2.5 mg, 5 mg, 10 mg, b.i.d.) in healthy volunteers resulted in mean plasma C_{max} values of 1.65 ng/mL (range: 0.9 - 2.4 ng/mL), 3.84 ng/mL (range: 1.5 - 6.1 ng/mL), and 7.95 ng/mL (range: 4.8 - 11.1 ng/mL) of 11-hydroxy Δ^9-THC, respectively (174). Time to reach C_{max} for 11-hydroxy Δ^9-THC ranged from 30 min - 4 h, with a mean of approximately 2.5 h (174). Importantly, 11-hydroxy Δ^9-THC has psychotomimetic properties equal to those of Δ^9-THC (276,313,314). The psycho-inactive 11-nor-9-carboxy Δ^9-THC is the primary acid metabolite of Δ^9-THC excreted in urine (315), and it is the cannabinoid often screened for in forensic analysis of body fluids (316,317).

CYP isozyme polymorphisms may also affect the pharmacokinetics of THC (and 11-nor-9-carboxy Δ^9-THC). For example, subjects homozygous for the *CYP2C9*3* allelic variant displayed significantly higher maximum plasma concentrations of Δ^9-THC, significantly higher area under the curve (AUC), and significantly decreased clearance among other measures compared to the *CYP2C9*1* homozygote or the **1/*3* heterozygote (318).

Xenobiotics are not only metabolized by CYPs but they also modulate the expression level and activity of these enzymes; CYPs are therefore a focal point in drug-drug interactions and adverse drug reactions (319). Polyaromatic hydrocarbons found in tobacco and cannabis smoke induce the expression of CYP1A2 (320), while Δ^9-THC, cannabidiol (CBD), and cannabinol (CBN) inhibit the activity of the CYP1A1, 1A2, and 1B1 enzymes (58). CBD has also been shown to inhibit the formation of Δ^9-THC metabolites catalyzed by CYP3A4, with less effect on CYP2C9 (301), albeit sufficiently to decrease the formation of 11-hydroxy THC (102,321).

Results from *in vitro* experiments also suggest that Δ^9-THC inhibits CYP3A4, CYP3A5, CYP2C9, and CYP2C19, while CBD inhibits CYP2C19, CYP3A4, and CYP3A5; however, higher concentrations than those seen clinically appear to be required for inhibition (58,290). While few clinical studies have specifically sought to evaluate cannabis-drug interactions *per se*, many, if not most, studies investigating the therapeutic effects of cannabis (e.g. smoked, vapourized, or orally ingested) and cannabinoid-based medicines (e.g. dronabinol, nabilone, nabiximols) have used patients that were concomitantly taking other medications (e.g. non-steroidal anti-inflammatory agents, opioids, anti-depressants, anti-convulsants, protease inhibitors) and, in general, did not report significantly increased incidences of severe adverse effects associated with the *combination* of cannabis or cannabinoids and these other medications. Nevertheless, clinicians should carefully monitor patients who are concomitantly consuming cannabis/cannabinoids and other medications that are metabolized by the above-mentioned enzymes.

The Sativex® product monograph cautions against combining Sativex® with amitriptyline or fentanyl (or related opioids) which are metabolized by CYP3A4 and 2C19 (290). Cannabis smoking, as well as orally administered dronabinol, may also affect the pharmacokinetics of anti-retroviral medications (322). In addition, and as seen with tobacco smoke, cannabis smoke has the potential to induce CYP1A2 thereby increasing the metabolism of xenobiotics biotransformed by this isozyme such as theophylline (323) or the anti-psychotic medicationsclozapine or olanzapine (324). **Further information on drug-drug interactions can be found in section 6.2.**

2.2.3.1 Inhalation

Plasma values of 11-hydroxy THC appear rapidly and peak shortly after Δ^9-THC, at about 15 min after the start of smoking (325). Peak plasma concentrations of 11-hydroxy THC 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 (312). Similar results were obtained with intravenous THC administration (326).

Peak plasma values of 11-nor-9-carboxy THC occur 1.5 - 2.5 h after smoking, and are about one third the concentration of parent THC (325). Following oxidation, the phase II metabolites of the free drug or hydroxy-THC appear to be glucuronide conjugates (272).

2.2.3.2 Oral

After oral doses of Δ^9-THC, parent THC and its active metabolite 11-hydroxy- Δ^9-THC (which is similar to or possibly greater in potency than Δ^9-THC) are present in approximately equal concentrations in plasma (276,286,327). The plasma levels of active 11-hydroxy metabolite, achieved through oral administration, are about three times higher than those seen with smoking (312). Concentrations of both parent drug and metabolite peak between approximately 2 - 4 h after oral dosing, and decline over several days. Whole-body clearance of Δ^9-THC and its hydroxy metabolite averages about 0.2 L/kg-h, but is highly variable due to the complexity of cannabinoid distribution (174).

2.2.4 Excretion

Δ^9-THC levels in plasma decrease rapidly after cessation of smoking. Mean THC plasma concentrations are approximately 60% and 20% of peak plasma THC concentrations 15 and 30 min post-smoking (328), respectively, and are below 5 ng/mL THC 2 h after smoking (276). Elimination of THC and its metabolites occurs via the feces (65%) and the urine (20%) (62). After five days, 80% to 90% of the total dose is excreted (312). Nevertheless, THC from a single dose can be detected in plasma up to 13 days in chronic smokers probably due to extensive storage and release from body fat (329).

Following oral administration, THC and its metabolites are also excreted in both the feces and the urine (312,62). Biliary excretion is the major route of elimination, with about half of a radiolabelled THC oral dose being recovered from the feces within 72 h in contrast to the 10 to 15% recovered from urine (312).

The decline of Δ^9-THC levels in plasma is multi-phasic, and the estimates of the terminal half-life of Δ^9-THC in humans have progressively increased as analytical methods have become more sensitive (301). While figures for the terminal elimination half-life of Δ^9-THC appear to vary, it is probably safe to say that it averages at least four days and could be considerably longer (62). The variability in terminal half-life measurements are related to the dependence of this measure on assay sensitivity, as well as on the duration and timing of blood measurements (330). Low levels of THC metabolites have been detected for more than five weeks in the urine and feces of cannabis users (301). The degree of Δ^9-THC consumption does not appear to influence the plasma half-life of Δ^9-THC (272,331).

2.3 Pharmacokinetic-pharmacodynamic relationships

Much of the information on cannabinoid pharmacokinetic-pharmacodynamic relationships (mostly on Δ^9-THC) is derived from studies of recreational cannabis use rather than from studies looking at therapeutic use, but in either case, this relationship depends to some extent on the point in time at which observations are made following the administration of the cannabinoid. Furthermore, the temporal relationship between plasma concentrations of Δ^9-THC and the associated clinical/therapeutic, psychotropic, cognitive and motor effects is not well established. These effects often lag behind the plasma concentrations of Δ^9-THC, and tolerance is known to develop to some of the effects but not to others ((101,151,330) and also see (187) and section 2.4 (Tolerance and Dependence)).

As mentioned above, the relationship between dose (and plasma concentration) versus response for possible therapeutic applications are ill-defined, except for some information obtained for oral dosing with dronabinol (synthetic Δ^9-THC, marketed as Marinol®), nabiximols (a botanical cannabis extract containing approximately equal concentrations of Δ^9-THC and CBD as well as other cannabinoids, terpenoids and flavonoids, marketed as Sativex®), or nabilone (synthetic Δ^9-THC, analog marketed as Cesamet®) for their limited indications (174,290,332). Interpretations of the pharmacokinetics of Δ^9-THC are also complicated by the presence of active metabolites, particularly the psychoactive 11-hydroxy THC, which are found in higher concentrations after oral administration than after inhalation (286,327).

Target Δ^9-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 blood plasma concentration estimates in the range of 7 - 29 ng/mL Δ^9-THC necessary for the production of a 50% maximal subjective "high" effect (330). Other studies suggest that Δ^9-THC plasma concentrations associated with 50% of the maximum "high" effect range between 2 and 250 ng/mL Δ^9-THC (median of 19 ng/mL; mean of 43 ng/mL Δ^9-THC) for the smoked or i.v. routes, while for the oral route the values range between 1 and 8 ng/mL Δ^9-THC (median and mean of 5 ng/mL Δ^9-THC) (111,333). 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 (133).

Smoked cannabis

Simulation of multiple dosing with a 1% THC cigarette containing 9 mg Δ^9-THC yielded a maximal "high" lasting approximately 45 min after initial dosing, declining to 50% of peak at about 100 min following smoking (151). A dosing interval of 1 h with this dose would give a "continuous high", and the recovery time after the last dose would be 150 min (i.e. 2.5 h). The peak Δ^9-THC plasma concentration during this dosage is estimated at about 70 ng/mL.

One clinical study reported a peak increase in heart rate and perceived "good drug effect" within 7 min after test subjects smoked a 1 g cannabis cigarette containing either 1.8% or 3.9% THC (mean doses of Δ^9-THC being 18 mg or

39 mg, respectively) (129). Compared to the placebo, both doses yielded statistically significant differences in subjective and physiological measures; the higher dose was also significantly different from the lower dose for subjective effects, but not physiological effects such as heart rate. Pharmacokinetic-pharmacodynamic modelling of concentration-effect relationship of Δ^9-THC on CNS parameters and heart rate suggests that THC-evoked effects typically lag behind THC plasma concentration, with the effects lasting significantly longer than Δ^9-THC plasma concentrations (334). The equilibration half-life estimate for heart rate was approximately 7 min, but varied between 39 and 85 min for various CNS parameters (334). According to this model, the effects on the CNS developed more slowly and lasted longer than the effect on heart rate.

The psychomotor performance, subjective, and physiological effects associated with whole-blood Δ^9-THC concentrations in heavy, chronic, cannabis smokers following an acute episode of cannabis smoking has been studied (280). Subjects reported smoking a mean of one joint per day in the previous 14 days prior to the initiation of the study (range 0.7 - 12 joints per day) (280). During the study, subjects smoked one cannabis cigarette (mean weight 0.79 ±0.16 g) containing 6.8 ±0.2% THC, 0.25 ±0.08% CBD, and 0.21 ±0.02% CBN (w/w) yielding a total THC, CBD, and CBN content of 54, 2.0, and 1.7 mg of these cannabinoids per cigarette (280). Mean peak THC blood concentrations and peak visual analog scale scores for different subjective measures occurred 15 min after starting smoking (280). According to the authors of the study, the pharmacodynamic-pharmacokinetic relationship described a counter-clockwise hysteresis (i.e. where for the same plasma concentration of a drug (e.g. THC), the pharmacological effect is greater at a later time point than at an earlier one) for all measured subjective effects (e.g. "good drug effect", "high", "stoned", "stimulated", "sedated", "anxious", and "restless"). This particular kind of relationship demonstrates a lack of correlation between blood concentrations of THC and observed effects, beginning immediately after the end of smoking and continuing during the initial distribution and elimination phases (280). All participants reported a peak subjective "high" between 66 and 85 on the visual analog scale, with peak whole blood THC concentrations at the time of these responses ranging from 13 - 63 ng/mL (280). Following the start of cannabis smoking, heart rate increased significantly at the 30 min time point, diastolic blood pressure decreased significantly only from the 30 min to 1 h time point, and systolic blood pressure and respiratory rate were unaffected at any time (280).

Oral and oro-mucosal cannabinoids

The subjective and physiological effects after controlled administration of nabiximols (Sativex®) or oral THC have also been compared (107). Increases in systolic blood pressure occurred with low (5 mg) and high (15 mg) oral doses of THC, as well as low (5.4 mg Δ^9-THC and 5 mg CBD) and high (16.2 mg Δ^9-THC and 15 mg CBD) dose nabiximols, with the effect peaking at around 3 h after administration (107). In contrast, diastolic blood pressure decreased between 4 and 8 h after dosing. Heart rate increased after all active treatments. A statistically significant increase in heart rate relative to placebo was observed after high-dose oral THC (15 mg Δ^9-THC) and high-dose nabiximols (16.2 mg Δ^9-THC and 15 mg CBD), but the authors indicated that the increases appeared to be less clinically significant than those typically seen with smoked cannabis (107). High-dose oral THC (15 mg Δ^9-THC) and high-dose nabiximols (16.2 mg Δ^9-THC and 15 mg CBD) were associated with significantly greater "good drug effects" compared to placebo, whereas low-dose nabiximols (5.4 mg Δ^9-THC and 5 mg CBD) was associated with significantly higher "good drug effects" compared to 5 mg THC (107). A subjective feeling of a "high" was reported to be significantly greater after 15 mg oral THC compared to placebo and to 5 mg oral THC. In contrast, neither the high nor the low doses of nabiximols were reported to produce a statistically significant subjective "high" feeling. Study subjects reported being most "anxious" approximately 4 h after administration of 5 mg oral THC, 3 h after 15 mg oral THC, 5.5 h after low-dose nabiximols, and 4.5 h after high-dose nabiximols (107). All active drug treatments induced significantly more anxiety compared to placebo. After 15 mg oral THC, the concentration of THC in plasma was observed to have a weak, but statistically significant, positive correlation with systolic and diastolic blood pressure, "good drug effect", and "high" (107). After high-dose nabiximols, positive correlations were also observed between plasma THC concentrations and "anxious", "good drug effect", "high", "stimulated", and M-scale (marihuana-scale) scores (107). Consistent with other studies, the authors of this study reported that linear correlations between plasma THC concentrations and physiological or subjective effects were weak. Lastly, although cannabidiol did not appear to significantly modulate the effects of THC, the authors suggested it may have attenuated the degree of the subjective "high" (107).

2.4. Tolerance, dependence, and withdrawal symptoms

Tolerance

Tolerance, as defined by the Liaison Committee on Pain and Addiction (a joint committee with representatives from the American Pain Society, the American Academy of Pain Medicine, and the American Society of Addiction Medicine) is a state of adaptation in which exposure to the drug causes changes that result in a diminution of one or more of the drug's effects over time (335).

Tolerance to the effects of cannabis or cannabinoids appears to result mostly from pharmacodynamic rather than pharmacokinetic mechanisms (211). Pre-clinical studies indicate that *pharmacodynamic* tolerance is mainly linked to changes in the availability of the cannabinoid receptors, principally the CB_1 receptor, to signal. There are two independent but interrelated molecular mechanisms producing these changes: receptor desensitization (or uncoupling of the receptor from intra-cellular downstream signal transduction events), and receptor downregulation (resulting from the internalization and/or degradation of the receptor) (336). Furthermore, within the brain, tolerance appears to vary across different regions suggesting cellular and tissue-specific mechanisms regulating desensitization/downregulation (see review by Gonzalez et al. (211)). This may also hold true for other tissues or organs, explaining why tolerance develops to some of the effects of cannabis and cannabinoids but not to other effects. In animal models, the degree and time-course of tolerance appear to depend on the species used, the type of cannabinoid ligand, the dosage and duration of the treatment, and the measures employed to determine tolerance (211). *Pharmacokinetic* tolerance (including changes in absorption, distribution, biotransformation and excretion) has also been documented, but apparently occurs to a lesser degree than pharmacodynamic tolerance (337). In the clinical setting, tolerance to the effects of cannabis or cannabinoids can potentially be minimized by combining lower doses of cannabis or cannabinoids along with one or more additional therapeutic drugs (338).

Tolerance to most of the effects of cannabis and cannabinoids can develop after a few doses, and it also disappears rapidly following cessation of administration (118). In normal subjects, tolerance develops to the effects of cannabis on mood, intra-ocular pressure, EEG, psychomotor performance, nausea, as well as on the cardiovascular system (212,213). There is also some evidence to suggest that tolerance can develop to the effects of cannabis on sleep (reviewed in (161)). As mentioned above, the dynamics of tolerance vary with respect to the different effects; tolerance to some of the effects develops more readily and rapidly than to others (214,215). A positron emission tomography imaging study of chronic daily cannabis smokers reported reversible and regionally selective downregulation of brain cannabinoid CB_1 receptors (339). This finding could help explain the results obtained from a previously published double-blind, randomized, placebo-controlled study which showed that subjects who reported frequently using cannabis (*frequently* being defined in this study as a positive toxicological test result for cannabis at screening, at least 10 exposures to cannabis immediately prior to study initiation, and meeting DSM-IV criteria for cannabis use disorder) displayed blunted responses to the psychotomimetic, perceptual altering, cognitive impairing, anxiogenic, and cortisol-increasing effects of THC compared to controls, but notably not to its euphoric effects (216). Another study reported that tolerance to some of the effects of cannabis, including tolerance to the "high", developed both when THC was administered orally (30 mg; four times per day; total daily dose 120 mg) (207) and when a roughly equivalent dose was given by smoking (3.1% THC cigarette; four times per day) (340). Interestingly, there was no diminution of the appetite-stimulating effect from either route of administration.

An uncontrolled, open-label extension study of an initial five-week randomized trial of nabiximols in patients with multiple sclerosis and central neuropathic pain reported the *absence* of pharmacological tolerance (measured by a change in the mean daily dosage of nabiximols), even after an almost two-year treatment period in a group of select patients (217). Another long-term, open-label extension study of nabiximols in patients with spasticity caused by multiple sclerosis echoed these findings, also reporting the *absence* of pharmacological tolerance (measured by a change in the mean daily dosage of nabiximols) after almost one year of treatment (218).

Dependence and withdrawal

Dependence can be divided into two independent, but in certain situations interrelated concepts: physical dependence and psychological dependence (i.e. addiction) (335). Physical dependence, as defined by the Liaison Committee on Pain and Addiction, is a state of adaptation manifested by a drug-class specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist (190). Psychological dependence (i.e. addiction) is a primary, chronic, neurobiological disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations, and is characterized by behaviours that include one or more of the following: impaired control over drug use, compulsive use, continued use

despite harm, and craving (335). 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 (341).

There is evidence that cannabis dependence (physical and psychological) occurs especially with chronic, heavy use (122,156,210). The endocannabinoid system has been implicated in the acquisition and maintenance of drug taking behaviour, and in various physiological and behavioural processes associated with psychological dependence or addiction (2). Physical dependence is most often manifested in the appearance of withdrawal symptoms when use is abruptly halted or discontinued. Withdrawal symptoms associated with cessation of cannabis use (oral or smoked) appear within the first one to two days following discontinuation; peak effects typically occur between days 2 and 6 and most symptoms resolve within 1 - 2 weeks (342). The most common symptoms include anger or aggression, irritability, anxiety, nightmares/strange dreams, insomnia/sleep difficulties, craving, headache, restlessness, and decreased appetite or weight loss (156,210,222). Other symptoms appear to include depressed mood, chills, stomach pain, shakiness and sweating (156,210,222).

3.0 Dosing

General remarks

Cannabis has many variables that do not fit well with the typical medical model for drug prescribing (277). The complex pharmacology of cannabinoids, interindividual (genetic) differences in cannabinoid receptor structure and function, interindividual (genetic) differences in cannabinoid metabolism affecting cannabinoid bioavailability, prior exposure to and experience with cannabis/cannabinoids, pharmacological tolerance to cannabinoids, changes to cannabinoid receptor distribution/density and/or function as a consequence of a medical disorder, the variable potency of the cannabis plant material, and the different dosing regimens and routes of administration used in different research studies all contribute to the difficulty in reporting precise doses or establishing uniform dosing schedules for cannabis (and/or cannabinoids) (277,328).

While precise dosages have not been established, some "rough" dosing guidelines for smoked or vapourized cannabis have been published (see below). Besides smoking and vapourization, cannabis is known to be consumed in baked goods such as cookies or brownies, or drunk as teas or infusions. However, absorption of these products by the oral route is slow and erratic, and the onset of effects is delayed with the effects lasting much longer compared to smoking (see section 2.2); furthermore, dosages for orally administered products are even less well established than for smoking/vapourization (111,286,289,343). Other forms of preparation reported in the lay literature include cannabis-based butters, oils, compresses, creams, ointments, and tinctures (64,344,345,346,347) but again, no dosing information exists here and much of the information is anecdotal in nature.

Dosing remains highly individualized and relies to a great extent on titration (277). Patients with no prior experience with cannabis and initiating cannabis 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. Consumption of smoked/inhaled or oral cannabis should proceed slowly, waiting between puffs for a few minutes and waiting 30 - 60 min between bites of cannabis-based oral products (e.g. cookies, baked goods) to gauge for strength of effects or for possible overdosing.

Minimal therapeutic dose and dosing ranges

Information obtained from the monograph for Marinol® (dronabinol) indicates that **a daily oral dose as low as 2.5 mg Δ^9-THC is associated with a therapeutic effect (e.g. treatment of AIDS-related anorexia/cachexia)**. Naturally, dosing will vary according to the underlying disorder and the many other variables mentioned above. Dosing ranges for Marinol® (dronabinol) vary from 2.5 mg - 40 mg Δ^9-THC/day (174). Dosing ranges for Cesamet® (nabilone) vary from 0.2 mg - 6 mg/day (332,348). Dosing ranges for Sativex® (nabiximols) vary from one spray (2.7 mg Δ^9-THC and 2.5 mg CBD) to 16 sprays (43.2 mg Δ^9-THC to 40 mg CBD) per day (290,349).

Various surveys published in the peer-reviewed literature have suggested that the majority of people using smoked or orally ingested cannabis for medical purposes reported using between 10 - 20 g of cannabis per week or approximately 1 - 3 g of cannabis per day (165,277,350).

Monitoring

Currently, there are no clinical guidelines on monitoring patients who are taking cannabis for medical purposes.

3.1 Smoking

According to the World Health Organization (WHO) (351), a typical joint contains between 0.5 and 1.0 g of cannabis plant matter (average weight = 750 mg) which may vary in Δ^9-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 Δ^9-THC delivered in the smoke varies widely and has been estimated at 20 - 70%, the remainder being lost through combustion or side-stream smoke (277). Furthermore, the bioavailability of Δ^9-THC (the fraction of Δ^9-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) (276). In addition, expectation of drug reward can also influence smoking dynamics (352). Thus, the actual dose of Δ^9-THC absorbed systemically when smoked is not easily quantified but has been approximated to be around 25% of the total available amount of Δ^9-THC in a cigarette (117,277).

Relationship between a smoked dose and an oral dose

Little information exists regarding conversion of a "smoked dose" of THC to an equivalent oral dose, however multiplication of a "smoked dose" of Δ^9-THC by a conversion factor of 2.5 (to correct for differences between the bioavailability of Δ^9-THC through the smoked route (~25%) vs. the oral route (~10%)) can yield an approximately equivalent oral dose of Δ^9-THC (117). The "smoked dose" can be defined as the dose, in mg, of Δ^9-THC that is available in the *cigarette*. As an example, smoking a cigarette containing 75 mg Δ^9-THC by weight (see **Row 4** in **Table 2** [10% Δ^9-THC, 750 mg dried plant material]) would yield an estimated oral dose of 187.5 mg Δ^9-THC (75 mg Δ^9-THC X 2.5 = 187.5 mg Δ^9-THC). Please consult **Tables 3, 4 and 5** for further information regarding converting between smoked and oral doses of Δ^9-THC.

Table 2: Relationship between THC Percent in Plant Material and the Available Dose (in mg THC) in an Average Joint

% THC	mg THC per 750 mg dried plant material* ("average joint")
1	7.5
2.5	18.75
5	37.5
10†	75†
15	112.5
20	150
30	225

* *WHO average weight*

† *see text in section 3.1 for additional details*

Table 3: Approximate Conversion Factors Smoked/Oral Δ^9-THC

	To Smoked Dose†	To Oral Dose‡
From Smoked Dose†		**Multiply** the dose of Δ^9-THC (in mg) in the dried plant material to be smoked by a factor of 2.5 to obtain the estimated dose of Δ^9-THC (in mg) to be ingested orally. (Smoked dose in mg X 2.5 = Oral dose in mg)
From Oral Dose‡	**Divide** the dose of Δ^9-THC (in mg) to be ingested orally by a factor of 2.5 to obtain the estimated dose of Δ^9-THC (in mg) to be smoked. (Oral dose in mg ÷ 2.5 = Smoked dose in mg)	

† A "smoked dose" can be defined as the total available amount of Δ^9-THC in a cannabis cigarette (calculated by multiplying the percentage of Δ^9-THC by the total gram amount of cannabis in the cigarette).
‡ An oral dose is defined as the total amount of Δ^9-THC that is ingested orally.

Table 4: Quick Reference of Smoked to Estimated Oral Doses of Δ^9-THC

"Smoked Dose"† % THC in a 750 mg cannabis cigarette (Total available mg Δ^9-THC)	**Estimated Oral Dose (mg Δ^9-THC)‡**
1 % THC (7.5 mg)	18.8 mg
2 % THC (15 mg)	37.5 mg
2.5 % THC (18.8 mg)	46.8 mg
3 % THC (22.5 mg)	56.3 mg
5 % THC (37.5 mg)	93.8 mg
7.5 % THC (56.3 mg)	140.6 mg
10 % THC (75 mg)	187.5 mg
12.5% THC (93.8 mg)	234.4 mg
15 % THC (112.5 mg)	281.3 mg
20 % THC (150 mg)	375 mg

† A "smoked dose" is defined as the total available amount (in mg) of Δ^9-THC in a standard cannabis cigarette (750 mg joint)
‡ An oral dose is defined as the total amount (in mg) of orally ingested Δ^9-THC

Numbers in the table are rounded to the nearest decimal place

Table 5: Quick Reference of Oral to Estimated Smoked Doses of Δ^9-THC

Oral Dose† (mg Δ^9-THC)	Estimated "Smoked Dose" ‡ (Total available mg Δ^9-THC in the dried plant material in the cigarette)
0.25	0.1
0.5	0.2
0.75	0.3
1	0.4
1.25	0.5
1.5	0.6
1.75	0.7
2	0.8
2.25	0.9
2.5	**1**
2.75	1.1
3	1.2
3.25	1.3
3.5	1.4
3.75	1.5
4	1.6
4.25	1.7
4.5	1.8
4.75	1.9
5	**2**
6	2.4
7	2.8
8	3.2
9	3.6
10	**4**
15	**6**
20	**8**
25	**10**
30	**12**
40	**16**
50	**20**
75	**30**
100	**40**

† An oral dose is defined as the total amount (in mg) of orally ingested Δ^9-THC
‡ A "smoked dose" is defined as the total available amount (in mg) of Δ^9-THC in a standard cannabis cigarette (750 mg joint)

Numbers in the table are rounded to the nearest decimal place

Table 6: Comparison between Cannabis and Prescription Cannabinoid Medications

Rx cannabinoids	Cannabinoid (Generic name)	Registered name	Principal constituents/ Source	Official status in Canada	Approved indications	Onset (O)/ Duration of action (D)	Route of admin.	Availability on provincial/ territorial formulary
	Dronabinol†	Marinol®†	Synthetic Δ^9-THC	Approved†	AIDS-related anorexia associated with weight loss; Severe nausea and vomiting associated with cancer chemotherapy	O: 30 - 60 min D: 4 - 6 h	Oral	MB†; NB†; NS†; ON†; PE†; QC†; YT†
	Nabilone	Cesamet®	Synthetic Δ^9-THC analogue	Approved	Severe nausea and vomiting associated with cancer chemotherapy	O: 60 - 90 min D: 8 - 12 h	Oral	AB; BC; MB; NB; NL; NS; NT; NU; ON; PE; QC; SK; YT.
	Nabiximols (THC+CBD and other minor cannabinoids, terpenoids, and flavonoids)	Sativex®	Botanical extract from established and well-characterized *C. sativa* strains	Approved *	*	O: 15 - 40 min D: 2 - 4 h	Oro-mucosal spray	NS.
Plant product	Cannabis (smoked)	N/A	*C. sativa (various)*	Not an approved product	N/A	O: 5 min D: 2 - 4 h	Smoking	N/A
	Cannabis (vapourized)	N/A	*C. sativa (various)*	Not an approved product	N/A	O: 5 min D: 2 - 4 h	Inhalation by vapourizer	N/A
	Cannabis (oral edible)	N/A	*C. sativa (various)*	Not an approved product	N/A	O: 30 - 60 min D: 8 - 12 h	Oral	N/A
	Cannabis (topical)	N/A	*C. sativa (various)*	Not an approved product	N/A	N/A	Topical	N/A

† Product has been discontinued by the manufacturer (post-market; as of February 2012; not for safety reasons)

*** For Sativex®, the following marketing authorizations apply:**

Standard marketing authorization: Adjunctive treatment for symptomatic relief of spasticity in adult patients with multiple sclerosis who have not responded adequately to other therapy and who demonstrate meaningful improvement during an initial trial of therapy.

Marketing authorization with conditions: Adjunctive treatment for symptomatic relief of neuropathic pain in adult patients with multiple sclerosis; and adjunctive analgesic treatment 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.

Plasma concentrations of Δ^9-THC following smoking

Using a paced smoking protocol, the mean plasma concentration of Δ^9-THC after a first inhalation of a cannabis cigarette containing 3.55% Δ^9-THC has been reported to be 18.1 ng/mL (range: 1.8 - 37.0 ng/mL), with the mean peak plasma concentration of Δ^9-THC reaching 162 ng/mL (range: 76 - 267 ng/mL) after seven puffs or almost complete smoking of the cigarette (276,328). Peak plasma concentrations of Δ^9-THC in the range of 50 - 100 ng/mL are associated with a subjective "high" ((279) and section 2.3) and can be easily attained by smoking a single 3.55% Δ^9-THC cannabis cigarette (900 mg plant material, 32 mg total available Δ^9-THC) (328). If the current average "street" marihuana contains 10% THC, joints from such a source might have an available 75 mg dose of Δ^9-THC and could result in rapid attainment of elevated plasma Δ^9-THC concentrations (> 100 ng/mL Δ^9-THC). More potent strains of cannabis could yield even higher plasma concentrations of THC.

Plasma concentrations of Δ^9-THC following smoking, and therapeutic efficacy

There are a small number of efficacy studies on the amounts of cannabis required for therapeutic effects (see **Table 7** for a quick overview, and information throughout this document for more detailed information). A Canadian dose-ranging study showed that a single inhalation of a 25 mg dose of smoked cannabis (Δ^9-THC content 9.4%; total available dose of Δ^9-THC = 2.35 mg) yielded a mean plasma Δ^9-THC concentration of 45 ng/mL within 2 min after initiating smoking (172). The study reported improvements in sleep and pain relief in patients suffering from chronic neuropathic pain (172). Using the above-mentioned conversion formula to translate smoked to estimated oral doses of Δ^9-THC, 2.35 mg Δ^9-THC in the dried plant material would correspond to an estimated oral dose of 5.9 mg Δ^9-THC.

Please consult **Tables 3, 4 and 5** for further information regarding converting between smoked and oral doses of Δ^9-THC. Please consult **Table 7** for a list of clinical trials of smoked cannabis and general details regarding those trials.

3.2 Oral

The pharmacokinetic information described in section 2.2.1.3 reports the erratic and slow absorption of Δ^9-THC from the oral route, and oral doses are estimated from the information in the monograph for Marinol® (dronabinol). A 10 mg b.i.d. dose of Marinol® (20 mg total Δ^9-THC per day) yielded a mean peak plasma Δ^9-THC concentration of 7.88 ng/mL (range: 3.33 - 12.42 ng/mL), with a bioavailability ranging between 10 and 20% (174). By comparison, consumption of a chocolate cookie containing 20 mg Δ^9-THC resulted in a mean peak plasma Δ^9-THC concentration of 7.5 ng/mL (range: 4.4 - 11 ng/mL), with a bioavailability of 6% (278). Tea prepared from *Cannabis* flowering tops and leaves has been documented, but no data are available regarding efficacy (289). To convert an oral dose to an estimated "smoked dose", the oral dose is divided by a conversion factor of 2.5 (117). Thus, an oral dose of 20 mg Δ^9-THC would be approximately equivalent to a "smoked dose" of 8 mg of Δ^9-THC. Please consult **Tables 3, 4 and 5** for further information regarding converting oral to smoked doses of Δ^9-THC.

Marinol

The Marinol® (dronabinol) product monograph suggests a mean of 5 mg Δ^9-THC/day (range: 2.5 - 20 mg Δ^9-THC/day) for AIDS-related anorexia associated with weight loss (174). A 2.5 mg dose may be administered before lunch, followed by a second 2.5 mg dose before supper. On the other hand, to reduce or prevent cancer chemotherapy-induced nausea or vomiting, a dosage of 5 mg t.i.d. or q.i.d. is suggested (174). In either case, the dose should be carefully titrated to avoid the manifestation of adverse effects. Please consult the drug product monograph for more detailed instructions.

Cesamet

The Cesamet® (nabilone) product monograph suggests administration of 1 - 2 mg of the drug, twice a day, with the first dose given the night before administration of the chemotherapeutic medication (332). A 2 mg dose of nabilone gave a mean plasma concentration of 10 ng/mL nabilone, 1 - 2 h after administration (332). The second dose is usually administered 1 - 3 h before chemotherapy. If required, the administration of nabilone can be continued up to 24 h after the chemotherapeutic agent is given. The maximum recommended daily dose is 6 mg in divided doses. Dose adjustment (titration) may be required in order to attain the desired response, or to improve tolerability. More recent clinical trials report starting doses of nabilone of 0.5 mg at night for pain or insomnia in fibromyalgia, and for insomnia in post-traumatic stress disorder (348,353,354). Please consult the drug product monograph for more detailed instructions.

Clinical studies with nabilone
A randomized, double-blind, placebo-controlled trial of nabilone in patients suffering from fibromyalgia reported that adjuvant nabilone therapy (four weeks; maximum dose in the final week of treatment: 1 mg b.i.d.) was associated with a significant improvement in measures of QoL (Visual Analogue Scale for pain, and the Fibromyalgia Impact Questionnaire) (353). An enriched-enrolment, randomized withdrawal, flexible-dose, double-blind, placebo-controlled, parallel-assignment efficacy study of nabilone as an adjuvant in the treatment of long-standing diabetic peripheral neuropathic pain reported statistically significant improvements in measures of QoL (Composite EQ-5D Index Score) and overall patient status compared to placebo (364). Doses of nabilone ranged from 1 - 4 mg/day; treatment duration was five weeks (364).

Clinical studies with nabiximols
A ten-week, prospective, randomized, double-blind, placebo-controlled trial assessing the safety and efficacy of nabiximols (Sativex®) as an adjunctive medication in the treatment of intractable diabetic peripheral neuropathy concluded that nabiximols failed to show statistically significant improvements in measures of QoL (EuroQOL, SF-36, and the McGill Pain and QOL Questionnaire) (365). A twelve-week, double-blind, randomized, placebo-controlled, parallel-group, enriched enrolment study of nabiximols as add-on therapy for patients with refractory spasticity concluded that there was no significant difference between active treatment and placebo on measures of QoL (EQ-5D Health State Index, EQ-5D Health Status VAS, SF-36) (366). A five-week, multi-centre, randomized, double-blind, placebo-controlled, parallel-group, graded-dose study evaluated the analgesic efficacy and safety of nabiximols in three dose ranges in opioid-treated cancer patients with poorly-controlled chronic pain (349). The study reported the lack of any positive treatment effects on overall QoL in this study population even at the highest doses of nabiximols (11 - 16 sprays per day) (349).

Clinical studies with smoked cannabis
A randomized, double-blind, placebo-controlled, four-period, cross-over trial of smoked cannabis in the treatment of chronic neuropathic pain (chronic post-traumatic or post-surgical etiology) concluded that inhalation of smoked cannabis (25 mg of cannabis containing 2.5, 6.0, or 9.4% Δ^9-THC, t.i.d. for five days) was not associated with a statistically significant difference compared to placebo on measures of QoL (EQ-5D Health Outcomes Quality of Life instrument) (172). In contrast, a cross-sectional survey examining the benefits associated with cannabis use in patients with fibromyalgia reported a statistically significant benefit in the mental health component summary score of the SF-36 Quality of Life questionnaire in patients who used cannabis compared to non-users (158). However, no significant differences between cannabis and non-cannabis users were found in the other SF-36 domains, in the Fibromyalgia Impact Questionnaire, or the Pittsburgh Sleep Quality Index (158).

A preliminary observational, open-label, prospective, single-arm trial in a group of 13 patients suffering from Crohn's disease or ulcerative colitis reported that treatment with inhaled cannabis over a three-month period improved subjects' quality of life, caused a statistically significant increase in subjects' weight, and improved the clinical disease activity index in patients with Crohn's disease (189). Patients reported a statistically significant improvement in their perception of their general health status, their ability to perform daily activities, and their ability to maintain a social life (189). Patients also reported a statistically significant reduction in physical pain as well as improvement in mental distress (189).

4.2 Nausea and vomiting

Chemotherapy-induced nausea and vomiting (CINV) is one of the most distressing and common adverse events associated with cancer treatment (367). While chemotherapy-induced vomiting generally appears to be well-controlled with current first-line therapies, the associated acute, delayed, or anticipatory nausea remain more poorly controlled and the use of cannabis/cannabinoids may provide some measure of benefit in certain cases (88,192). It is important to note that excessive use of cannabis has been reported to paradoxically trigger a chronic cyclic vomiting syndrome (i.e. hyperemesis) (see section 7.6.1 for further details on this syndrome).

Pre-clinical studies

Patient claims that smoked cannabis relieves CINV are widely recognized, and increasing evidence suggests a role for the endocannabinoid system in the regulation of nausea and vomiting (88). Cannabinoid CB_1 and CB_2 receptors have been found in areas of the brainstem associated with emetogenic control (368,369), and results from animal studies suggest the anti-nausea and anti-emetic properties of cannabinoids (e.g. Δ^9-THC, dronabinol, nabilone) are most likely related to their agonistic actions at CB_1 receptors (80,88,370). An *in vivo* animal study and one small clinical study

have also suggested Δ^8-THC to be a more potent anti-emetic than Δ^9-THC (80,81). In addition to its actions at CB_1 receptors, an *in vitro* study has also shown that Δ^9-THC antagonizes the 5-HT_3 receptor (371), a target of standard anti-emetic drugs, raising the possibility that cannabinoids may exert their anti-emetic action through more than one mechanism. More recently, studies carried out in animal models of nausea and vomiting have shown that cannabidiol (5 mg/kg, s.c.) suppressed nicotine, lithium chloride, and cisplatin-induced vomiting in the shrew; lithium chloride-induced conditioned gaping was suppressed in rats through a yet-to-be identified, but probably indirect, activation of somatodendritic 5-HT_{1A} autoreceptors located in the dorsal raphe nucleus (372). Another study showed that the anti-nausea/vomiting effects of cannabidiol could be reversed by pre-treatment with cannabigerol (5 mg/kg, i.p.) (373).

Clinical studies

The evidence for cannabinoids such as nabilone (Cesamet®), dronabinol (Marinol®), and levonantradol in treating CINV has been reviewed (159,374). While cannabinoids present clear advantages over placebo in the control of CINV, the evidence from randomized clinical trials shows cannabinoids to be clinically only slightly better than conventional dopamine D2-receptor antagonist anti-emetics (159,374). 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. This may be explained in part by the notion that for certain patients a degree of sedation and euphoria may be perceived as beneficial during chemotherapy.

While no peer-reviewed clinical trials of smoked cannabis for the treatment of CINV exist, Musty and Rossi have published a review of U.S. state clinical trials on the subject (191). Patients who smoked cannabis showed a 70 - 100% relief from nausea and vomiting, while those who used a Δ^9-THC capsule experienced 76 - 88% relief (191). Plasma levels of > 10 ng/mL Δ^9-THC were associated with the greatest suppression of nausea and vomiting, although levels ranging between 5 and 10 ng/mL were also effective (191). In all cases, patients were admitted only after they failed treatment with standard phenothiazine anti-emetics. A small clinical trial comparing smoked cannabis (2.11% Δ^9-THC, in doses of 8.4 mg or 16.9 mg Δ^9-THC; 0.30% cannabinol; 0.05% cannabidiol) to ondansetron (8 mg) in ipecac-induced nausea and vomiting in healthy volunteers showed that both doses of Δ^9-THC reduced subjective ratings of queasiness and objective measures of vomiting; however, the effects were very modest compared to ondansetron (192). Furthermore, only cannabis produced changes in mood and subjective state.

Few, if any, clinical trials directly comparing cannabinoids to newer anti-emetics such as 5-HT_3 (Ondansetron, Granisetron) or NK-1 receptor antagonists have been reported to date (367,374). In one clinical study with a small sample size, ondansetron and dronabinol (2.5 mg Δ^9-THC first day, 10 mg second day, 10 - 20 mg thereafter) provided equal relief of delayed CINV, and the combination of dronabinol and ondansetron did not provide added benefit beyond that observed with either agent alone (375). However, two animal studies showed that low doses of Δ^9-THC, when combined with low doses of the 5-HT_3 receptor antagonists ondansetron or tropisetron, were more efficacious in reducing nausea and emesis frequency than when administered individually (376,377). More research is required to determine if combination therapy provides added benefits above those observed with newer standard treatments.

The use of cannabinoids (whether administered orally or by smoking cannabis) is currently considered a fourth-line adjunctive therapy in CINV when conventional anti-emetic therapies have failed (285,378,379,380,381,382). Nabilone (Cesamet®) and dronabinol (Marinol®) are indicated for the management of severe nausea and vomiting associated with cancer chemotherapy (174,332). Nabilone may be administered orally every 12 h at dosages ranging from 1 - 2 mg, whereas dronabinol may be administered every 6 - 8 h orally, rectally, or sub-lingually at doses ranging from 5 - 10 mg (208,383).

The current Marihuana Medical Access Regulations (MMAR) allow the use of dried marihuana in the context of cancer chemotherapy-associated nausea and vomiting as well as nausea and vomiting associated with HIV/AIDS infection in patients who have either not benefited from, or would not be considered to benefit from, conventional treatments (384).

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

The ability of cannabis to increase appetite has been recognized anecdotally for many years (206). In addition, results from epidemiological studies suggest that people actively using cannabis have higher intakes of energy and nutrients than non-users (385). Controlled laboratory studies with healthy subjects suggest exposure to cannabis, whether by inhalation or oral ingestion of Δ^9-THC-containing capsules, correlates positively with an increase in food consumption, caloric intake, and body weight (205,206). Studies showing a high concentration of CB_1 receptors in brain areas associated with control of food intake and satiety lend further support to the link between cannabis consumption and appetite regulation (386,387,388). Furthermore, increasing evidence suggests a role for the endocannabinoid system not only in modulating appetite, food palatability, and intake, but also in energy metabolism and the modulation of both lipid and glucose metabolism (reviewed in (17,387,388,389)).

4.3.1 To stimulate appetite and produce weight gain in AIDS patients

The ability of cannabis 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 (166) showed that experienced HIV+ cannabis smokers with clinically significant muscle mass loss benefited from both dronabinol (four to eight times the standard 2.5 mg Δ^9-THC b.i.d dose, or 10 - 20 mg Δ^9-THC daily, three times per week for a total of eight sessions) and smoked cannabis (three puffs at 40 sec intervals; ~800 mg cigarettes containing 1.8 - 3.9% THC giving an estimated total daily amount of 14.4 mg - 31.2 mg THC *in the cigarette*, three times per week, for a total of eight study sessions). A subsequent study employed even higher doses of dronabinol (20 - 40 mg total Δ^9-THC daily, for a total of four days) and smoked cannabis (~800 mg cannabis cigarettes containing 2 and 3.0% THC, administered four times per day, giving an estimated 64 - 125 mg total Δ^9-THC daily *in the cigarette*, for a total of four days) (167). Both drugs produced substantial and comparable increases in food intake and body weight, as well as improvements in mood and sleep (166,167). The cannabis-associated increase in body weight appeared to result from an increase in body fat rather than lean muscle mass (390,391). On the other hand, a randomized, open-label, multi-center study to assess the safety and pharmacokinetics of dronabinol and megestrol acetate (an orexigenic), alone or in combination, found that only the high-dose megestrol acetate treatment alone (750 mg/day), but not dronabinol (2.5 mg b.i.d, 5 mg total Δ^9-THC/day) alone or the combination of low-dose megestrol acetate (250 mg/day) and dronabinol (2.5 mg b.i.d, 5 mg total Δ^9-THC/day), produced a significant increase in mean weight over 12 weeks of treatment in patients diagnosed with HIV-associated wasting syndrome (392). The lack of an observed clinical effect in this study could have been caused by too low a dose of dronabinol.

AIDS-related anorexia associated with weight loss is an approved indication in Canada for dronabinol (Marinol®). The Marinol® product monograph summarizes a six-week, 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) (393). Over the 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 (394). This secondary, 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 (394). The use of higher doses of dronabinol (20 mg - 40 mg per day) has been reported both in the Marinol® product monograph (174) as well as in the literature (166,167). However, caution should be exercised in escalating dosage because of the increased frequency of dose-related adverse effects.

The current Marihuana Medical Access Regulations (MMAR) allow the use of dried marihuana in the context of HIV/AIDS-associated anorexia, cachexia, and weight loss in patients who have either not benefited from, or would not be considered to benefit from, conventional treatments (384).

4.3.2 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 (395,396). While it is anecdotally known that smoking cannabis can stimulate appetite, the effects of smoking cannabis on appetite and weight gain in patients with cancer cachexia have not been studied. The results from trials with oral Δ^9-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 (397,398). An open-label study of dronabinol (2.5 mg Δ^9-THC, two to three times daily, four to six 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 (399,400). Modest weight gain was obtained with a larger dosing regimen of dronabinol (5 mg t.i.d.), but the CNS side effects including dizziness and somnolence were limiting factors (401). 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, Δ^9-THC, or placebo) (363). Furthermore, when compared to megestrol acetate, an orexigenic medication, dronabinol was significantly less efficacious in reported appetite improvement and weight gain (402). According to a recent review of the medical management of cancer cachexia, the current level of evidence for cannabinoids (e.g. dronabinol) in the treatment of this condition is low (403).

A two-centre, phase II, randomized, double-blind, placebo-controlled, 22-day pilot study carried out in adult patients suffering from advanced cancer reported improved and enhanced chemosensory perception among patients treated with dronabinol (2.5 mg Δ^9-THC b.i.d.) compared to those receiving placebo (362). The majority (73%) of dronabinol-treated patients self-reported an increased overall appreciation of food compared to those receiving placebo (30%). Similarly, the majority of dronabinol-treated patients (64%) reported increased appetite, whereas the majority of patients receiving placebo reported either decreased appetite (50%) or no change (20%). Total caloric intake per kilogram body weight did not differ significantly between treatment groups but did increase in both groups compared to baseline. Furthermore, compared to placebo, dronabinol-treated patients reported an increase in their protein intake as a proportion of total energy. According to the study authors, negative psychoactive effects were minimized by starting patients at a low dose (2.5 mg Δ^9-THC once a day, for three days) followed by gradual dose escalation (up to a maximum of 7.5 mg dronabinol per day) (362).

Cancer cachexia is not an approved indication for dronabinol either in Canada or the U.S. The current Marihuana Medical Access Regulations (MMAR) allow the use of dried marihuana in the context of anorexia, cachexia and weight loss associated with cancer in patients who have either not benefited from, or would not be considered to benefit from, conventional treatments (384).

4.3.3 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 (387,404). However, genetic studies have thus far failed to agree on an association between genes coding for endocannabinoid system proteins and the manifestation of anorexia nervosa, in spite of epidemiological and familial studies which suggest a genetic basis for this disorder (405,406).

Little information exists on the use of cannabinoids to treat anorexia nervosa. Inter- and intra-species differences in animals with respect to anorexia nervosa-like behaviour have to some extent hampered research on the effects of Δ^9-THC in this disorder. One study in a mouse model of anorexia nervosa reported conflicting results (407), while another study in a rat model reported a significant attenuation in weight loss only at high doses of Δ^9-THC (2.0 mg/kg/day Δ^9-THC) (408). A small, randomized, crossover trial of oral THC in female anorexic patients suggested that Δ^9-THC produced a weight gain equivalent to the active placebo (diazepam) (409). Δ^9-THC was administered in daily doses increasing from 7.5 mg (2.5 mg, t.i.d.) to a maximum of 30 mg (10 mg, t.i.d.), 90 min before meals, for a period of two weeks. Three of the eleven patients administered Δ^9-THC also reported severe dysphoric reactions, withdrawing from the study. Another small clinical study of 15 patients with dementia of the Alzheimer-type reported increases in body weight, but no change in caloric intake with dronabinol (2.5 mg Δ^9-THC, b.i.d.) compared to placebo (410). However, the study suffered from a number of limitations and the results should be interpreted with caution. No studies have examined the effects of smoking cannabis on anorexia nervosa. Both the British Medical Association (115) and the Institute of Medicine (378) concluded that cannabis was unlikely to be effective in patients with anorexia nervosa; however, further research may be warranted.

4.4 Multiple sclerosis, amyotrophic lateral sclerosis, spinal cord injury

Anecdotal reports suggest cannabis can ameliorate spasticity in patients suffering from multiple sclerosis or spinal cord injury when other drugs fail or produce unacceptable side effects (115,378,411,412,413).

4.4.1 Multiple sclerosis

A number of studies, both in patients suffering from multiple sclerosis (MS) and in animal models of the disease, suggest the disorder is associated with changes in endocannabinoid levels, although the findings are conflicting (414,415,416,417).

Pre-clinical studies

Pre-clinical studies across different animal species suggest cannabinoids improve the signs of motor dysfunction in experimental models of MS (reviewed in (418)). Lyman was one of the first to report the effects of Δ^9-THC in one such model (419). In that study, affected animals treated with Δ^9-THC either had no clinical signs of the disorder or showed mild clinical signs with delayed onset (419). The treated animals also typically had a marked reduction in central nervous system tissue inflammation compared to untreated animals (419). Subsequent studies in murine models of MS have supported and extended these findings demonstrating that Δ^9-THC, but not cannabidiol, ameliorated both tremor and spasticity and reduced the overall clinical severity of the disease (414,420). Further work highlighted the importance of the CB_1 receptor in controlling tremor, spasticity, and the neuroinflammatory response. In contrast, the exact function of the CB_2 receptor in MS remains somewhat unclear, although it is believed to play a role in regulating the neuroinflammatory response (420,421,422). Although a large body of evidence suggests cannabinoids exert immunosuppressive effects, which could be beneficial in diseases such as MS, much of this information comes from pre-clinical studies where the levels of exogenous cannabinoids given to animals would likely exceed those typically administered to patients (422). Therefore it is believed that the beneficial effects of cannabinoids are more likely to come from their neuroprotective properties rather than their immunosuppressive characteristics (422,423,424).

Historical and survey data

In humans, published reports spanning 100 years suggest that people with spasticity (one of the symptoms associated with MS) may experience relief with cannabis (425). 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 (426). In Canada, the prevalence of medicinal use of cannabis among patients seeking treatment for MS, in the year 2000, was reported to be 16% in Alberta, with 43% of study respondents stating they had used cannabis at some point in their lives (164). Fourteen percent of people with MS surveyed in the year 2002 in Nova Scotia reported using cannabis for medical purposes, with 36% reporting ever having used cannabis for any purpose (165). MS patients reported using cannabis to manage symptoms such as spasticity and chronic pain as well as anxiety and/or depression (164,165). MS patients also reported improvements in sleep. Reputed dosages of smoked cannabis by these patients varied from a few puffs to 1 g or more at a time (165).

Clinical studies with orally administered cannabinoid medications (cannabis extract, oral THC, nabiximols)

The results of randomized, placebo-controlled trials with orally administered cannabinoids for the treatment of muscle spasticity in MS are encouraging, but modest.

The large, multi-centre, 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 (262). The primary outcome was change in overall spasticity scores measured using the Ashworth scale. The study did not show any statistically significant improvement in the Ashworth score in patients taking either an oral cannabis extract (("Cannador") containing 2.5 mg Δ^9-THC, 1.25 mg CBD, and < 5% other cannabinoids), or oral Δ^9-THC, for 15 weeks. However, there was evidence of a significant treatment effect on *subjective, patient-reported* spasticity and pain, with improvement in spasticity using either orally administered cannabis extract (61%) (Dosing: 5 - 25 mg Δ^9-THC; 5 - 15 mg CBD/day; and < 5% other cannabinoids, adjusted to body weight and titrated according to side effects) or oral Δ^9-THC (60%) (Dosing: 10 - 25 mg Δ^9-THC/day, adjusted to body weight and titrated according to side effects) compared to placebo (46%). Patients were concomitantly taking other medications to manage MS-associated symptoms. In contrast, a long-term (12 months), double-blind, follow-up to the CAMS study showed evidence of a small treatment effect of oral Δ^9-THC (Dosing: 5 - 25 mg Δ^9-THC/day, adjusted to body weight and titrated according to side effects) on

muscle spasticity measured by *objective* methods, whereas a *subjective* treatment effect on muscle spasticity was observed for both oral Δ^9-THC and oral cannabis extract ("Cannador") (427).

Other randomized clinical trials using standardized cannabis extract capsules (containing 2.5 mg Δ^9-THC and 0.9 mg CBD per capsule) (428) or nabiximols (Sativex®) (291,429,430) reported similar results, in that improvements were only seen in patient *self-reports* of symptoms but not with *objective* measures (e.g. Ashworth scale). The reasons behind the apparent discrepancies between subjective and objective measures are not clear; however, a number of possible explanations may be found to account for the differences. For example, it is known that spasticity is a complex phenomenon (431) and is affected by patient symptoms, physical functioning, and psychological disposition (427). Spasticity is also inherently difficult to measure, and has no single defining feature (430). In addition, the reliability and sensitivity of the Ashworth scale (for objectively measuring spasticity) has been called into question (262,430).

The efficacy, safety, and tolerability of a whole-plant cannabis extract administered in capsules (2.5 mg THC and 0.9 mg CBD/capsule) were studied in a fourteen-day, prospective, randomized, double-blind, placebo-controlled crossover trial in patients with clinically stable MS-associated spasticity and an Ashworth score greater than 2 (428). Slightly more than half of the study subjects had a maintenance dose of 20 mg/day of THC or more (maximum of 30 mg THC/day). Patients were concomitantly taking anti-spasticity medications. Many study subjects had had previous experience with cannabis; a significant number of those who withdrew from the study upon starting treatment with the cannabis extract did not have previous experience with cannabis. While there were no statistically significant differences between active treatment with the cannabis extract and placebo, trends in favour of active treatment were observed for mobility, *self-reported* spasm frequency, and ability in getting to sleep (428). The cannabis extract was generally well tolerated with no serious adverse events during the study period. However, adverse events were slightly more frequent and more severe during the active treatment period.

A six-week, multi-centre, randomized, double-blind, placebo-controlled, parallel-group study of nabiximols (Sativex®) for the treatment of five primary symptoms associated with MS (spasticity, spasm frequency, bladder problems, tremor, and pain) reported mixed results (291). Patients had clinically confirmed, stable MS of any type, and were on a stable medication regimen. Approximately half of the study subjects in either the active or placebo groups had previous experience with cannabis, either recreationally or for medical purposes. While the global primary symptom score (PSS), which combined the scores for all five symptoms, was not significantly different between the active treatment group and the placebo group, patients taking cannabis extract showed statistically significant differences compared to placebo in *subjective*, but not objective measures of spasticity (i.e. Ashworth Score), in Guy's Neurological Disability Score (GNDS), and in quality of sleep, but not in spasm frequency, pain, tremor, or bladder problems among other outcome measures (291). Patients self-titrated to an average daily maintenance dose of nabiximols of 40.5 mg THC and 37.5 mg CBD (i.e. ~15 sprays/day). Adverse effects associated with active treatment included dizziness, disturbance in attention, fatigue, disorientation, feeling drunk, and vertigo (291).

A long-term, open-label, follow-up study of nabiximols (Sativex®) concluded that the beneficial effect observed in the study by Wade et al. 2004 (291) was maintained in patients who had initially benefited from the drug (429). The mean duration of study participation in subjects who entered the follow-up study was 434 days (range: 21 - 814 days). The average number of daily doses taken by the subjects remained constant or was slightly reduced over time. The average number of daily doses of nabiximols was 11, corresponding to a dose of 30 mg THC and 28 mg CBD/day (429). Long-term use of nabiximols in this patient population was associated with reductions in *subjective* measures of spasticity, spasm frequency, pain, and bladder problems (429). Dizziness, diarrhea, nausea, fatigue, headache, and somnolence were among the most frequently reported adverse effects associated with chronic nabiximols use in this study. A two-week withdrawal study, incorporated into the long-term follow-up study, suggested that cessation of nabiximols use was not associated with a consistent withdrawal syndrome but it was associated with withdrawal-type symptoms (e.g. interrupted sleep, hot/cold flushes, fatigue, low mood, decreased appetite, emotional lability, vivid dreams, intoxication) as well as re-emergence/worsening of some MS symptoms (429).

The efficacy, safety and tolerability of nabiximols in MS were investigated in a six-week, multi-centre, phase III, double-blind, randomized, parallel-group clinical study in patients with stable MS who had failed to gain adequate relief using standard therapeutic approaches (430). Patients had to have significant spasticity in at least two muscle groups, and an Ashworth score of 2 or more. A significant number of patients had previous experience with cannabis. Forty percent of subjects assigned treatment with nabiximols showed a $\geq$ 30% reduction in self-

reported spasticity using an 11-point *subjective* numerical rating spasticity scale (NRS) compared to subjects assigned to placebo (21.9%) (difference in favour of nabiximols = 18%; 95% Confidence Interval = 4.73, 31.52; $p = 0.014$). Mean number of sprays per day was 9.4 ±6.4 (~25 mg THC and ~24 mg CBD) (430). Subjects on placebo or nabiximols exhibited similar incidences of adverse effects, but adverse CNS effects were more common with the nabiximols group (430). The majority of adverse events were of mild or moderate severity (e.g. dizziness, fatigue, depressed mood, disorientation, dysgeusia, disturbance in attention, blurred vision).

Nabiximols (Sativex®), an oro-mucosal spray containing 27 mg/mL of Δ^9-THC and 25 mg/mL CBD, is currently marketed in Canada as an adjunctive treatment for the symptomatic relief of spasticity in adult patients with MS who have not responded adequately to other therapy and who demonstrate meaningful improvement during an initial trial of therapy. It is also marketed (with conditions) as an adjunctive treatment for the symptomatic relief of neuropathic pain in adults with MS.

CUPID and MUSEC clinical studies

The CUPID (**C**annabinoid **U**se in **P**rogressive **I**nflammatory **B**rain **D**isease) study was a randomized, double-blind, clinical investigation designed to measure whether orally administered Δ^9-THC was able to slow the progression of MS (http://sites.pcmd.ac.uk/cnrg/cupid.php). This three-year publicly-funded trial took place at the Peninsula Medical School in the U.K. and followed the earlier, one-year long, CAMS study. A total of 493 subjects with primary or secondary progressive, but not relapse-remitting, MS had been recruited from across the U.K. in 2006 and preliminary results were recently made public (http://sites.pcmd.ac.uk/cnrg/files/cupid/CUPID_results_press_release_web.pdf). The CUPID trial found no evidence to support an effect of Δ^9-THC on MS progression, as measured by using either the Expanded Disability Status Scale or the Multiple Sclerosis Impact Scale 29 (MSIS-29). However, the authors concluded that there was some evidence to suggest a beneficial effect in participants who were at the *lower end* of the disability scale at the time of patient enrolment. Since the observed benefit only occurred in a small sub-group of patients, further studies would be required to more closely examine the reasons for this selective effect.

A double-blind, placebo-controlled, phase III study (the **MU**ltiple **S**clerosis and **E**xtract of **C**annabis trial—i.e. "MUSEC") published by the same group of researchers that conducted the CUPID trial, reported that a twelve-week treatment with an oral cannabis extract ("Cannador") (2.5 mg Δ^9–THC and 0.9 mg CBD/capsule) was associated with a statistically significant relief in *patient-reported* muscle stiffness, muscle spasms, and body pain as well as a statistically significant improvement in sleep compared to placebo, in patients with stable MS (432). There were no statistically significant differences between cannabis extract and placebo on functional measures such as those examining the effect of spasticity on activities of daily living, ability to walk, or on social functioning (432). The majority of the patients using cannabis extract used total daily doses of 10, 15, or 25 mg of Δ^9–THC with corresponding doses of 3.6, 5.4, and 9 mg of CBD. The majority of the study subjects were concomitantly using analgesics and anti-spasticity medications, but were excluded if they were using immunomodulatory medications (e.g. interferons). Active treatment with the extract was associated with an increase in the number of adverse events, but the majority of these were considered to be mild to moderate and did not persist beyond the study period (432). The highest number of adverse events were observed during the initial two-week titration period and appeared to decrease progressively over the course of the remaining treatment sessions (432). The most commonly observed adverse events were those associated with disturbances in CNS function (e.g. dizziness, disturbance in attention, balance disorder, somnolence, feeling abnormal, disorientation, confusion, and falls). Disturbances in gastrointestinal function were the second most commonly occurring adverse events (e.g. nausea, dry mouth).

Clinical studies with smoked cannabis

There has only been one clinical study so far using smoked cannabis for symptoms associated with MS (188). The study, a double-blind, placebo-controlled, crossover trial reported a statistically significant reduction in patient scores on the modified Ashworth scale for measuring spasticity after patients smoked cannabis once daily for three days (each cigarette contained 800 mg of 4% Δ^9-THC; total available Δ^9-THC dose of 32 mg per cigarette) (188). Smoking cannabis was also associated with a statistically significant reduction in patient scores on the visual analog scale for pain, although patients reportedly had low levels of pain to begin with (188). No differences between placebo and cannabis were observed in the timed-walk task, a measure of physical performance (188). Cognitive function, as assessed by the Paced Auditory Serial Addition Test (PASAT), appeared to be significantly decreased immediately following administration of cannabis; however, the long-term clinical significance of this finding was not examined in this study (188). The majority of patients (70%) were on disease-modifying therapy (e.g. interferon β-1a, interferon β-1b, or glatiramer), and 60% were taking anti-

spasticity agents (e.g. baclofen or tizanidine). Cannabis treatment was associated with a number of different, but commonly observed adverse effects including dizziness, headache, fatigue, nausea, feeling "too high", and throat irritation (188). Study limitations included the fact that the majority of patients had prior experience with cannabis, and that the study was unblinded since most of the patients were able to tell apart the placebo from the active treatment with cannabis (188).

The current Marihuana Medical Access Regulations (MMAR) allow the use of dried marihuana in the context of severe pain and persistent muscle spasms associated with MS in patients who have either not benefited from, or would not be considered to benefit from, conventional treatments (384).

Generally speaking, orally administered prescription cannabinoids (e.g. dronabinol, nabilone, nabiximols) are reported to be well tolerated in patients with MS (428,433,434). Clinical trials to date do not indicate serious adverse effects associated with the use of these prescription cannabinoid medications. However, there appears to be an increase in the number of non-serious adverse effects associated with the short-term use of cannabinoids (4). The most commonly reported short-term physical adverse effects are dizziness, drowsiness, and dry mouth (262,434). Prolonged use of ingested or inhaled cannabis was associated with poorer performance on various cognitive domains (information processing speed, working memory, executive function, and visuospatial perception) in patients with MS according to one cross-sectional study (178). In contrast, another study concluded that nabiximols (Sativex®) treatment, in cannabis-naïve MS patients, was not associated with cognitive impairment (434). 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. In any case, important information is generally lacking regarding the long-term adverse effects of chronic cannabinoid use for therapeutic purposes.

Bladder dysfunction associated with multiple sclerosis or spinal cord injury

Bladder dysfunction occurs in most patients suffering from multiple sclerosis (MS) or spinal cord injury (435). The most common complaints are increased urinary frequency, urgency, urge, and reflex incontinence (436). Cannabinoid receptors are expressed in human bladder detrusor and urothelium (35,36), and may help regulate detrusor tone and bladder contraction as well as affecting bladder nociceptive response pathways (reviewed in (36)).

A survey of MS patients regularly using cannabis for symptomatic relief of urinary problems reported that over half of these patients claimed improvement in urinary urgency (437). A sixteen-week, open-label, pilot study of cannabis-based extracts (a course of Sativex® treatment followed by maintenance with 2.5 mg Δ^9-THC only) for bladder dysfunction, in 15 patients with advanced MS, reported significant decreases in urinary urgency, number and volume of incontinence episodes, frequency, and nocturia (438). 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 cannabinoids (2.5 mg Δ^9-THC or 1.25 mg cannabidiol (CBD) with < 5% other cannabinoids per capsule, up to a maximum 25 mg/day) on incontinence episodes (435).

4.4.2 Amyotrophic lateral sclerosis

There is some pre-clinical evidence implicating the endocannabinoid system in the progression of an amyotrophic lateral sclerosis (ALS)-like disease in mouse models of the disorder, and under certain conditions cannabinoids have been reported to modestly delay disease progression and prolong survival in these animal models (reviewed in (439) and in (440)). Anecdotal reports suggest decreased muscle cramps and fasciculations in ALS patients who smoked herbal cannabis or drank cannabis tea, with up to 10% of these patients using cannabis for symptom control (441,442). Only two clinical trials of cannabis for the treatment of symptoms associated with ALS exist, and the results of the studies are mixed. In one four-week, randomized, double-blind, crossover pilot study of 19 ALS patients, doses of 2.5 - 10 mg per day of dronabinol (Δ^9-THC) were associated with improvements in sleep and appetite, but not cramps or fasciculations (443). In contrast, a shorter two-week study reported no improvement in these measures in ALS patients taking 10 mg of dronabinol per day (442). In either case, dronabinol was well tolerated with few reported side effects in this patient population at the tested dosages.

4.4.3 Spinal cord injury (or spinal cord disease)

Pre-clinical animal studies suggest that spinal cord injury triggers changes in the activity of the endocannabinoid system, and that cannabinoid receptor agonists may alleviate neuropathic pain associated with spinal cord injury (444,445,446). However, limited clinical information exists regarding the use of cannabinoids to treat symptoms associated with spinal cord injury such as pain, spasticity, muscle spasms, urinary incontinence, and difficulties

sleeping. No clinical trials of smoked cannabis for the treatment of these symptoms have been documented, but subjective improvements have been anecdotally reported by patients smoking cannabis (378,447). Double-blind, crossover, placebo-controlled studies of oral Δ^9-THC and/or Δ^9-THC : CBD extract (Sativex®) suggested modest improvements in pain, spasticity, muscle spasms, and sleep quality in patients with spinal cord injury (378,448,449). A randomized, double-blind, placebo-controlled parallel study using a minimum of 15 - 20 mg Δ^9-THC/day (mean daily doses of 31 mg Δ^9-THC orally, or 43 mg Δ^9-THC-hemisuccinate rectally) showed a statistically significant improvement in spasticity scores in patients with spinal cord injury (450). A more recent double-blind, placebo-controlled, crossover study using nabilone (0.5 mg b.i.d.) also showed an improvement in spasticity compared to placebo in patients with spinal cord injury (451).

The current Marihuana Medical Access Regulations (MMAR) allow the use of dried marihuana in the context of severe pain and persistent muscle spasms associated with spinal cord injury or spinal cord disease in patients who have either not benefited from, or would not be considered to benefit from, conventional treatments (384).

4.5 Epilepsy

Increasing evidence points to a role for the endocannabinoid system in the modulation of neuronal tone and excitability, and possibly in epilepsy. Human and animal studies suggest epileptic activity is associated with changes in the levels and distribution of CB_1 receptors in the hippocampus (452,453,454). Reduced levels of the endocannabinoid anandamide have been detected in the cerebrospinal fluid of patients with untreated, newly diagnosed, temporal lobe epilepsy (455).

Pre-clinical studies

In vitro studies, as well as those carried out in animals, generally suggest an anti-convulsant role for cannabinoids (91,456,457,458,459). However, a pro-convulsant role has also been described (91,460). CB_1 receptors are located mainly pre-synaptically where they typically inhibit the release of classical neurotransmitters (461). The purported anti-epileptic effect of cannabinoids is thought to be mediated by CB_1-receptor dependent pre-synaptic inhibition of glutamate release (453,462); on the other hand, epileptogenic effects may be triggered by pre-synaptic inhibition of GABA release (456,457,459,463,464). CB_1 receptor agonists therefore have the potential to trigger or suppress epileptiform activity depending upon which cannabinoid-sensitive pre-synaptic terminals are preferentially affected (i.e. glutamatergic or GABAergic) (91,462).

Clinical studies

A review of the literature describing the effects of cannabis 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 (465). This may be caused by the rather unspecific actions of exogenously administered cannabinoids, such as Δ^9-THC, which would target both excitatory and inhibitory neurons (91). Cannabidiol (CBD) has also been examined as a potential anti-epileptic in humans (see (466) for full review) but these early studies have not been followed up with larger and more convincing clinical trials. A recent Cochrane Collaboration review aimed at assessing the efficacy and safety of cannabinoids as monotherapy or add-on treatment for patients with epilepsy concluded that the available evidence is not sufficient to be able to draw reliable conclusions regarding the efficacy of cannabinoids as a treatment for epilepsy (467). While a dose of 200 - 300 mg of CBD could be safely administered to a small number of patients for a short period of time, the safety of long-term cannabidiol treatment could not be reliably assessed (467).

The current Marihuana Medical Access Regulations (MMAR) allow the use of dried marihuana in the context of epilepsy in patients who experience seizures and who have either not benefited from, or would not be considered to benefit from, conventional treatments (384).

4.6 Pain

It is now well established that the endocannabinoid system plays an important role in the modulation of pain states and that elements of the endocannabinoid system can be found at supraspinal, spinal, and peripheral levels of pain pathways (22,468). The particular distribution of cannabinoid receptors provides an anatomical basis to explain some of the analgesic effects of cannabinoids, and a number of pre-clinical studies suggest a functional role for endocannabinoids (such as anandamide and 2-arachidonoylglycerol (i.e. 2-AG)) in suppressing pain under physiological conditions (22).

Considerations and caveats

Animal vs. human studies

Pre-clinical studies in animals predict that cannabinoids should relieve both acute and chronic pain. However, results from both experimental models of pain in human volunteers and from clinical trials of patients suffering from pain instead suggest cannabinoids may be more effective for chronic rather than acute pain (469,470,471). A number of possible explanations can exist to account for discrepancies between animal studies and human clinical trials. Such explanations include interspecies differences, differences in experimental stimuli and protocols used in the studies, and differences in the outcomes measured in the studies. Data from animal pain models are mostly based on observations of behavioural changes and cannabinoid doses sufficient to produce relevant anti-nociception in rodents are similar to those which cause other behavioural effects such as hypomotility and catatonia (21,472). This pharmacological overlap can make it difficult to distinguish between cannabinoid-associated anti-nociceptive effects and behavioural effects (21,472).

Experimental models of pain vs. chronic pain

Translation of research findings from human experimental models of pain (i.e. acute pain) to clinical pain is also complex and not straightforward (185). In contrast to acute pain, chronic pain is a complex condition which involves interaction between sensory, affective, and cognitive components (185). Unlike acute pain, chronic pain is considered a disease and generally originates from prolonged acute pain which is not managed in a timely or effective manner (473). Chronic pain also appears to involve distinct spatiotemporal neuronal mechanisms which differ from those recruited during acute, experimental pain (474). Chronic pain involves altered neural transmission and long-term plasticity changes in the peripheral and central nervous systems which generate and maintain the chronic pain state (473,474). As such, it is difficult to compare studies of interventions for chronic pain with studies of experimentally-induced pain because of fundamental differences in the physiological state of the subjects, differences in the stimulus conditions and experimental protocols employed in the studies, and differences in the outcomes which are measured (185).

Placebo effect

The placebo effect is another consideration to keep in mind when considering studies of cannabis/cannabinoids for the treatment of pain. The placebo effect, a psychobiological phenomenon, is perhaps more salient in disorders which have a more significant subjective or psychological component (e.g. pain, anxiety/depression), and may be somewhat less salient in diseases which have a more objective pathophysiological component (e.g. infectious diseases, cancer) (475,476).

Patient/study subject population

Many, if not most, of the clinical trials of cannabinoids for the treatment of pain (and even other disorders such as multiple sclerosis) have recruited patients or volunteers who have had prior exposure or experience with cannabis or cannabinoids. This has raised the issue of unblinding because any study subjects having prior experience with cannabis or cannabinoids would be more likely to be able to distinguish active treatment with these drugs from the placebo control (364). Furthermore, a number of clinical trials of cannabis/cannabinoids for the treatment of pain (or other disorders) have also used an "open-phase" period which eliminated subjects who would have either responded poorly to cannabinoids or who would have had greater chances of experiencing adverse effects (48). The use of individuals with prior experience with cannabis or cannabinoids or the use of an "open-phase" period would increase the proportion of patients yielding results tending to overestimate some of the potential therapeutic benefits of cannabis/cannabinoids, while also tending to underestimate the extent or degree of adverse effects among the general patient population (48,364).

Other considerations

It is also perhaps worth mentioning that a number of clinical studies suggest the presence of a relatively narrow therapeutic window for cannabis and prescription cannabinoids in the treatment of pain (21,48,50,472). The well-known psychotropic and somatic side effects effects associated with the use of cannabis and cannabinoids (e.g.

dronabinol, nabilone, nabiximols) are known to limit the general therapeutic utility of these drugs; it has therefore been suggested that it may be preferable to pursue therapies which focus on manipulation of the endocannabinoid system (e.g. by inhibiting the endocannabinoid-degrading enzymes FAAH or MAGL), or to combine low doses of cannabinoids with low doses of other analgesics in order to achieve the desired therapeutic effects while minimizing the incidence, frequency, and severity of the adverse effects (21,50).

With the above considerations and caveats in mind, the sections below summarize the results of studies examining the analgesic potential of cannabis or cannabinoids in pre-clinical and clinical models of experimentally-induced acute pain, as well as in clinical studies of chronic pain.

4.6.1. Acute Pain

4.6.1.1 Experimentally-induced acute pain

Pre-clinical studies

A number of pre-clinical studies suggest that anandamide, THC, and certain synthetic cannabinoids block pain responses in different animal models of acute pain (reviewed in (21,472)). Cannabinergic modulation of neuronal circuits in the brain and spinal cord can inhibit nociceptive processing (477,478,479,480). However, despite the results obtained in pre-clinical studies, the results of studies using cannabis or cannabinoids (e.g. nabilone) to alleviate experimentally-induced acute pain in humans are mixed.

Clinical studies with smoked cannabis

An early study by Hill of 26 healthy male cannabis smokers failed to demonstrate an analgesic effect of smoked cannabis (1.4% Δ^9-THC, 12 mg available Δ^9-THC) in response to transcutaneous electrical stimulation (481). The study did, however, report an *increase* in sensory and pain sensitivity to the applied stimulus. In contrast, Milstein showed that smoked cannabis (1.3% Δ^9-THC, 7.5 mg total available Δ^9-THC) increased pain tolerance to a pressure stimulus in both healthy cannabis-naïve and cannabis-experienced subjects compared to placebo (482). Another study employing healthy cannabis smokers reported that smoking cannabis cigarettes (containing 3.55% Δ^9-THC, or approximately 62 mg available Δ^9-THC) was associated with a mild, dose-dependent, anti-nociceptive effect to a thermal heat stimulus (184). A more recent randomized, double-blind, placebo-controlled, crossover trial examined the effects of three different doses of smoked cannabis on intra-dermal capsaicin-induced pain and hyperalgesia in 15 healthy volunteers (185). Capsaicin was administered either 5 min or 45 min after smoking cannabis. Effects appeared to be dose and time dependent. No effect was observed 5 min after smoking, but analgesia was observed 45 min after smoking, and only with the medium dose of smoked cannabis (4% Δ^9-THC by weight). A low dose (2% Δ^9-THC by weight) had no effect. In contrast, a high dose (8% Δ^9-THC by weight) was associated with significant *hyperalgesia*. This study identified a so-called "narrow therapeutic window"; a medium dose provided analgesic benefit, a high dose worsened the pain and was associated with additional adverse effects, and a low dose had no effect.

Clinical studies with oral THC and cannabis extract

A randomized, placebo-controlled, double-blind, crossover study of 12 healthy cannabis-naïve volunteers administered a single oral dose of 20 mg Δ^9-THC reported a lack of a significant analgesic effect following exposure to a multi-model pain test battery (pressure, heat, cold, and transcutaneous electrical stimulation) (483). In addition, significant hyperalgesia was observed in the heat pain test. Psychotropic and somatic side effects were common and included anxiety, perceptual changes, hallucinations, strange thoughts, ideas and mood, confusion and disorientation, euphoria, nausea, headache, and dizziness. Another randomized, double-blind, active placebo-controlled, crossover study in 18 healthy female volunteers reported a lack of analgesia or anti-hyperalgesia with an oral cannabis extract containing 20 mg THC and 10 mg CBD (other plant cannabinoids were less than 5%) in two different experimental pain models (intra-dermal capsaicin or sunburn) (484). Side effects (sedation, nausea, and dizziness) were frequently observed. Hyperalgesia was also observed at the highest dose as in the study conducted by Wallace (above) (185).

Clinical studies with nabilone

A randomized, double-blind, placebo-controlled, crossover study of single oral doses of nabilone (0.5 mg or 1 mg) failed to show any analgesic effects during a tonic heat pain stimulus (485). However, an anti-hyperalgesic effect was observed at the highest administered dose, but only in female subjects. The authors noted a significant placebo effect and also suggested that the lack of an analgesic effect could have been

attributed to the single-dose administration of the cannabinoid; a gradual dose escalation could have potentially revealed an effect (485). Similarly, a randomized, double-blind, placebo-controlled, crossover study in subjects receiving single oral doses of nabilone (1, 2, or 3 mg) failed to show any analgesic, or primary or secondary anti-hyperalgesic effects in response to capsaicin-induced pain in healthy male volunteers (355). Adverse effects of mild to moderate intensity were noted in the majority of subjects. Severe adverse reactions (e.g. dizziness, sedation, anxiety, agitation, euphoria, and perceptual and cognitive disturbances) were reported only at the highest administered dose (3 mg) in four subjects leading to their withdrawal from the study. Dose-dependent CNS effects were observed 1.5 - 6 h after dosing, reaching a maximum between 4 and 6 h after administration. A recent review suggests that there is little convincing evidence of a significant reduction in acute pain in human experimental or clinical studies of cannabinoids (21).

4.6.1.2 Post-operative pain

Despite the introduction of new standards, guidelines, and educational efforts, data indicate that post-operative pain continues to be under or poorly managed and many of the drugs commonly used in this setting either lack sufficient efficacy or cause unacceptable side effects (486,487). To date, there are only four published reports on the use of cannabinoids in post-operative pain (486,488,489,490). The conclusions from these studies were that cannabinoids (THC, nabilone, or an oral cannabis extract containing a 2 : 1 ratio of THC to CBD) are not ideally suited to manage post-operative pain, being either moderately effective (486,488), not different from placebo (489), or even anti-analgesic at high doses (490). However, a definitive conclusion on the role of these cannabinoids in the post-operative setting cannot yet be made because of the different drugs, dosages, routes of administration, and protocols that were used in these studies (491).

4.6.2 Chronic Pain

Acute pain that is poorly managed can lead to chronic pain (492,493). In contrast to acute pain, chronic pain is typically considered a far more complex condition which involves physical, psychological, and psychosocial factors, and which contributes to a reduced quality of life (494). The information below summarizes pre-clinical studies carried out in animal models of chronic pain, clinical studies in human subjects suffering from chronic pain of various etiologies, as well as some studies of experimentally-induced pain performed on patients.

4.6.2.1 Experimentally-induced pain

The anti-nociceptive efficacy of cannabinoids has been unequivocally demonstrated in several different animal models of inflammatory and neuropathic pain (reviewed in (495) and in (496)). In addition, the findings from these studies suggest that modulation of the endocannabinoid system through administration of specific cannabinoid receptor agonists, or by elevation of endocannabinoid levels, suppresses hyperalgesia and allodynia induced by diverse neuropathic states (reviewed in (496)). As such, similar to the situation with acute pain, pre-clinical studies of chronic pain in animal models suggest that endocannabinoids (anandamide and 2-AG), THC, and several synthetic cannabinoids have beneficial effects (reviewed in (21,472,496)).

With respect to cannabidiol (CBD), while chronic oral administration of cannabidiol effectively decreased hyperalgesia in a rat model of inflammatory pain (497), no such parallels have been found to date in humans. A more recent study suggested that a medium or a high dose of CBD attenuates tactile allodynia and thermal hypersensitivity in a mouse model of diabetic neuropathy, when administered early in the course of the disease; on the other hand there is little, if any, restorative effect if CBD is administered at a later time point (498). In contrast, nabilone was not as efficacious as CBD if administered early on, but appeared to have a small beneficial effect when administered later in the course of the disease (498). CBD also appeared to attenuate microgliosis in the ventral lumbar spinal cord, but only if administered early in the course of the disease, whereas nabilone had no effect (498).

There are no studies of experimentally-induced chronic pain in humans. However, in contrast to the mixed findings in human subjects exposed to acute painful stimuli, cannabinoids appear to have a more consistent beneficial profile for patients already suffering from chronic pain.

4.6.2.2 Neuropathic pain or chronic non-cancer pain

Short-term clinical studies suggest prescription cannabinoid medications (e.g. nabiximols, dronabinol, nabilone) are moderately effective in reducing intractable central or peripheral neuropathic pain of various etiologies in individuals already receiving analgesic drugs (499). Side effects appear to be comparable to

existing treatments and typically include dizziness/lightheadedness, sedation, confusion, ataxia, a feeling of intoxication, euphoria ("high"), xerostomia, dysgeusia, and hunger (499,500). These effects may be minimized by employing low doses of cannabinoids that are gradually escalated, as required. The following summarizes the existing clinical information on the use of cannabis and cannabinoids (THC, nabilone, dronabinol and nabiximols) to treat neuropathic and chronic non-cancer pain.

Clinical studies with smoked or vapourized cannabis

A randomized, double-blind, placebo-controlled, cross-over study of cannabis-experienced patients suffering from chronic neuropathic pain of various etiologies (complex regional pain syndrome, central neuropathic pain from spinal cord injury or multiple sclerosis, or peripheral neuropathic pain from diabetes or nerve injury) reported that administration of either a low dose or a high dose of smoked cannabis (3.5% Δ^9-THC, 19 mg total available Δ^9-THC; or 7% Δ^9-THC, 34 mg total available Δ^9-THC) was associated with significant equianalgesic decreases in central and peripheral neuropathic pain (168). No analgesic effect was observed in tests of experimentally-induced pain (tactile or heat stimuli). Patients were taking other pain control medications during the trial such as opioids, anti-depressants, non-steroidal anti-inflammatory drugs, or anti-convulsants. Adverse effects associated with the use of cannabis appeared to be dose-dependent and included feeling "high", sedation, confusion, and neurocognitive impairment. Cognitive changes appeared to be more pronounced with higher doses of Δ^9-THC (168).

In another randomized, placebo-controlled study a greater than 30% decrease in HIV-associated sensory neuropathic pain was reported in 52% of cannabis-experienced patients smoking cannabis cigarettes containing 3.56% Δ^9-THC (32 mg total available Δ^9-THC per cigarette), three times per day (96 mg total daily amount of Δ^9-THC) for five days, compared to a 24% decrease in pain in the placebo group (142). The number of patients that needed to be treated (NNT) to observe a 30% reduction in pain compared to controls was 3.6 and was comparable to that reported for other analgesics in the treatment of chronic neuropathic pain. In the "experimentally-induced pain" portion of the study, smoked cannabis was not associated with a statistically significant difference in acute heat pain threshold compared to placebo. However, it did appear to reduce the area of heat and capsaicin-induced acute secondary hyperalgesia (142). Patients were taking other pain control medications during the trial such as opioids, gabapentin or other drugs. Adverse effects of smoked cannabis in this study included sedation, dizziness, confusion, anxiety, and disorientation.

A phase II, double-blind, placebo-controlled, crossover clinical trial of smoked cannabis for HIV-associated refractory neuropathic pain reported a 30% decrease in HIV-associated, distal sensory predominant, polyneuropathic pain in 46% of patients smoking cannabis for five days (1 - 8% Δ^9-THC, four times daily), compared to a decrease of 18% in the placebo group (186). The NNT in this study was 3.5. Almost all of the subjects had prior experience with cannabis and were concomitantly taking other analgesics such as opioids, non-steroidal anti-inflammatory drugs, anti-depressants or anti-convulsants. Adverse effects associated with the use of cannabis were reported to be frequent, with a trend for moderate or severe adverse effects during the active treatment phase compared to the placebo phase.

A randomized, double-blind, placebo-controlled, four period, crossover clinical study of smoked cannabis for chronic neuropathic pain caused by trauma or surgery and refractory to conventional therapies reported that compared to placebo, a single smoked inhalation of 25 mg of cannabis containing 9.4% Δ^9-THC (2.35 mg total available Δ^9-THC per cigarette), three times per day (7.05 mg total Δ^9-THC per day) for five days, was associated with a modest but statistically significant decrease in average daily pain intensity (172). In addition, there were statistically significant improvements in measures of sleep quality and anxiety with cannabis. The majority of subjects had previous experience with cannabis and most were concomitantly taking other analgesics such as opioids, anti-depressants, anti-convulsants, or non-steroidal anti-inflammatory drugs. Adverse effects associated with the use of cannabis included headache, dry eyes, burning sensation in the upper airways (throat), dizziness, numbness, and cough.

A clinical study of patients suffering from chronic pain (musculoskeletal, post-traumatic, arthritic, peripheral neuropathy, cancer, fibromyalgia, multiple sclerosis, sickle cell disease, and thoracic outlet syndrome) reported that inhalation of vapourized cannabis (0.9 g, 3.56% Δ^9-THC), three times per day for five days, was associated with a statistically significant decrease in pain (-27%, Confidence Interval = 9 - 46) (187). Subjects were on stable doses of sustained-release morphine sulfate or oxycodone, and had prior experience with smoking cannabis (187). There was a statistically significant decrease in the maximum concentration (C_{max}) of morphine sulfate, but not oxycodone, during cannabis exposure. No clinically significant adverse

effects were noted, but all subjects reported experiencing a "high". The study design carried a number of important limitations including small sample size, short duration, a non-randomized subject population, and the lack of a placebo.

A double-blind, placebo-controlled, crossover study of patients suffering from neuropathic pain of various etiologies (spinal cord injury, CRPS type I, causalgia-CRPS type II, diabetic neuropathy, multiple sclerosis, post-herpetic neuralgia, idiopathic peripheral neuropathy, brachial plexopathy, lumbosacral radiculopathy, and post-stroke neuropathy) reported that inhalation of vapourized cannabis (0.8 g containing either a low dose of Δ^9-THC (1.29% Δ^9-THC; total available amount of Δ^9-THC 10.3 mg) or a medium dose of Δ^9-THC (3.53% Δ^9-THC; total available amount of Δ^9-THC 28.2 mg)) during three separate 6 h sessions was associated with a statistically significant reduction in pain intensity (501). Inhalation proceeded using a standardized protocol (i.e. the "Foltin procedure"): participants were verbally signaled to hold the vapourizer bag with one hand, put the vapourizer mouthpiece in their mouth, get ready, inhale (5 s), hold vapour in their lungs (10 s), and finally exhale and wait before repeating the inhalation cycle (40 s) (501). Non-significant differences were observed between placebo and active treatments with respect to pain ratings at the 60 min time point following study session initiation. Following four cued inhalations of either dose of THC at the 60 min time point, a significant treatment effect was recorded 60 min later (i.e. at the 120 min time point following trial initiation). A second cued inhalation of vapourized cannabis, at the 180 min time point following trial initiation (4 - 8 puffs, flexible dosing, 2 h after first inhalation), was associated with continued analgesia lasting another 2 h (501). Both the 1.29% and 3.53% Δ^9-THC doses were equianalgesic and significantly better in achieving analgesia than placebo. The NNT to achieve a 30% pain reduction was 3.2 for the placebo vs. the low-dose, 2.9 for the placebo vs. the medium-dose, and 29 for the medium- vs. the low-dose (501). The authors suggested that the NNT for active vs. placebo conditions is in the range of two commonly used anti-convulsants used to treat neuropathic pain (pregabalin, 3.9; gabapentin, 3.8). Using a Global Impression of Change rating scale, pain relief appeared to be maximal after the second dosing at 180 min, and dropped off between 1 and 2 h later. Both active doses had equal effects on ratings of pain "sharpness", while the low-dose was more effective than either the placebo or medium-dose for pain described as "burning" or "aching". All patients had prior experience with cannabis and were concomitantly taking other medications (opioids, anti-convulsants, anti-depressants, and non-steroidal anti-inflammatory drugs) (501). Cannabis treatment was associated with a small impairment of certain cognitive functions, with the greatest effects seen in domains of learning and memory (501). The study suffered from a number of drawbacks including a relatively small number of patients, a short study period, and the possibility of treatment unblinding.

Clinical studies with orally administered prescription cannabinoids

Nabilone

An off-label, retrospective, descriptive study of 20 adult patients suffering from chronic non-cancer pain of various etiologies (post-operative or traumatic pain, reflex sympathetic dystrophy, arthritis, Crohn's disease, neuropathic pain, interstitial cystitis, HIV-associated myopathy, post-polio syndrome, idiopathic inguinal pain, and chronic headaches) reported subjective overall improvement and reduced pain intensity with nabilone as an adjunctive pain-relief therapy (494). Furthermore, beneficial effects on sleep and nausea were the main reasons for continuing use. Patients used between 1 and 2 mg of nabilone per day. Higher doses (3 - 4 mg/day) were associated with an increased incidence of adverse effects. These included dry mouth, headaches, nausea and vomiting, fatigue, cognitive impairment, dizziness, and drowsiness. Many patients were concomitantly taking other drugs such as non-steroidal anti-inflammatory drugs, opioids, and various types of anti-depressants. Many of the subjects also reported having used cannabis in the past to manage symptoms. Limitations in study design included the lack of an appropriate control group and the small number of patients.

An enriched-enrolment, randomized-withdrawal, flexible-dose, double-blind, placebo-controlled, parallel-assignment efficacy study of nabilone as an adjuvant in the treatment of diabetic peripheral neuropathic pain reported a statistically significant decrease in pain compared to placebo, with 85% of the subjects in the nabilone group reporting a $\geq$ 30% reduction in pain from baseline to end point, and 31% of subjects in the nabilone group reporting a $\geq$ 50% reduction in pain from baseline to end point (364). Subjects taking nabilone also reported statistically significant improvements in anxiety, sleep, quality of life, and overall patient status (364). Doses of nabilone ranged from 1 - 4 mg/day (364). Most subjects were concomitantly taking a variety

of pain medications including non-steroidal anti-inflammatory drugs, opioids, anti-depressants, and anxiolytics. Adverse events associated with the nabilone intervention included dizziness, dry mouth, drowsiness, confusion, impaired memory, lethargy, euphoria, headache, and increased appetite although weight gain was not observed (364).

Dronabinol

A randomized, double-blind, placebo-controlled, crossover trial of patients suffering from multiple sclerosis-associated central neuropathic pain reported a decrease in central pain with 10 mg maximum daily doses of dronabinol (361). Dosing started with 2.5 mg dronabinol/day and employed gradual dose-escalation every other day; total trial duration was three weeks (range: 18 - 21 days). Pain medications, other than paracetamol, were not permitted during the trial. The NNT for 50% pain reduction was 3.5 (95% Confidence Interval = 1.9 to 24.8). Fifty-four percent of patients had a $\geq$ 33% reduction in pain during dronabinol treatment compared with 21% of patients during placebo. The degree of pain reduction in this study was comparable to that seen with other drugs commonly used in the treatment of neuropathic pain conditions (361). There were no significant differences reported between the treatment group and placebo in thermal sensibility, tactile and pain detection, vibration sense, temporal summation, or mechanical or cold allodynia (361). However, there was a statistically significant increase in the pain pressure threshold in dronabinol-treated subjects. Self-reported adverse effects were common, especially during the first week of active treatment. These included lightheadedness, dizziness, drowsiness, headache, myalgia, muscle weakness, dry mouth, palpitations, and euphoria (361).

A phase I, randomized, single-dose, double-blind, placebo-controlled, crossover trial of 30 patients taking short- or long-acting opioids (68 mg oral morphine equivalents/day; range 7.5 - 228 mg) for intractable, chronic non-cancer pain (of various etiologies) reported that both a 10 mg and 20 mg dose of dronabinol was associated with significant pain relief compared to placebo, although no difference in pain relief was observed between the two active treatments (502). Pain intensity and evoked pain were also significantly reduced in subjects who received the active treatments compared to placebo. Significant pain relief compared to baseline was also reported in an open-label, phase II extension to the initial phase I trial. Subjects were instructed in a stepwise dosage schedule beginning with a 5 mg/day dose, and titrating upwards to a maximum of 20 mg t.i.d. Significant side effects were observed in the majority of patients in the single-dose trial, were consistent with those observed in other clinical trials, and occurred more frequently in subjects receiving the highest dosage of the study medication (502). The authors reported that compared to the single-dose phase I trial, the frequency of self-reported side effects in the phase II open-label study decreased with continued use of dronabinol. Limitations in the design of the study included the small number of study subjects, the large number of subjects with a history of cannabis use, the lack of appropriate comparison groups, and the lack of an active placebo. Other limitations specific to the open-label phase-II trial included the lack of a control group or crossover arm (502).

Nabiximols

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 (e.g. brachial plexus avulsion, multiple sclerosis-related) following treatment with nabiximols (Sativex®) (292,503,504). In all three studies, patients were concomitantly using other drugs to manage their pain (anti-epileptics, tricyclic anti-depressants, opioids, non-steroidal anti-inflammatory drugs, selective serotonin reuptake inhibitors, benzodiazepines, skeletal muscle relaxants). 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 8.5 for peripheral pain. In two of the three studies, the majority of subjects had prior experience with cannabis for therapeutic or recreational purposes (503,504). Furthermore, the majority of subjects allocated to the active treatment experienced minor to moderate adverse effects compared to the placebo group. These included nausea, vomiting, constipation, dizziness, intoxication, fatigue, and dry mouth among other effects.

According to the consensus statement and clinical guidelines on the pharmacological management of chronic neuropathic pain published by the Canadian Pain Society in 2007, the Society considered cannabinoid-based therapies (e.g. dronabinol and nabiximols) to be fourth-line treatments for neuropathic pain, mostly as adjuvant analgesics for pain conditions refractory to standard drugs (505) (but also see section 4.7.3 and reference (506) for updated clinical guidelines on the use of cannabinoids for the treatment of symptoms associated with fibromyalgia). Health Canada has approved Sativex® (with conditions) as an adjunct treatment for the symptomatic relief of neuropathic pain in multiple sclerosis (290).

A Canadian systematic review of randomized clinical trials of cannabinoids (cannabis, nabilone, dronabinol and nabiximols) for the treatment of chronic non-cancer pain (neuropathic pain, mixed chronic pain, rheumatoid arthritis, fibromyalgia) concluded that cannabinoids are modestly effective for neuropathic pain, with preliminary evidence of efficacy in rheumatoid arthritis (see section 4.7.2) and fibromyalgia (see section 4.7.3) (173). Major limitations identified in the review were short trial duration, small sample sizes, and modest effect sizes, with a need for larger trials of longer duration to better establish efficacy and safety as well as potential for abuse.

4.6.2.3 Cancer pain

Clinical studies with dronabinol

Two randomized, double-blind, placebo-controlled studies suggested oral Δ^9-THC (dronabinol) provided an analgesic benefit in patients suffering from moderate to severe continuous pain due to advanced cancer. The first study was a dose-ranging study of 5, 10, 15, and 20 mg Δ^9-THC, given in successive days, to 10 cancer patients (507). 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 compared 10 and 20 mg oral Δ^9-THC with 60 and 120 mg codeine in 36 patients with cancer pain (508). 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 Δ^9-THC, and between placebo and 120 mg codeine. The 10 mg Δ^9-THC dose was well tolerated, and despite its sedative effect appeared to have mild analgesic potential. The 20 mg Δ^9-THC dose induced somnolence, dizziness, ataxia, and blurred vision. Extreme anxiety was also observed at the 20 mg dose in a number of patients.

Clinical studies with nabiximols

A more recent randomized, double-blind, placebo-controlled, parallel-group trial of patients suffering from intractable cancer-related pain (mixed, bone, neuropathic, visceral, somatic/incident) suggested that an orally administered THC : CBD extract (nabiximols), containing 2.7 mg of Δ^9-THC and 2.5 mg CBD per dose, is an efficacious adjunctive treatment for such cancer-related pain which is not fully relieved by strong opioids (112). Baseline median morphine equivalents/day ranged from 80 - 120 mg. Forty-three percent of patients (n = 60) taking the extract achieved a $\geq$ 30% improvement in their pain score, which was twice the number of patients who achieved this response in the THC (n = 58) and placebo (n = 59) groups. Both the nabiximols and the THC medications were reported to be well tolerated in this patient population, and adverse events were reported to be similar to those seen in other clinical trials of nabiximols (e.g. somnolence, dizziness, and nausea). This study was followed-up by an open-label extension study which evaluated the long-term safety and tolerability of nabiximols (as well as oro-mucosal THC spray) as an adjuvant pain treatment in patients with terminal cancer-related pain refractory to strong opioid analgesics (509). Patients who had taken part in, fully complied with the study requirements of, had not experienced an unacceptable adverse event in the initial parent study (112), and that were expected to receive clinical benefit from nabiximols (with acceptable tolerability) were enrolled in the extension study. The most commonly reported (50%) pain type was mixed pain (nociceptive and neuropathic), followed by neuropathic pain (37%), and bone pain (28%) (509). The median duration of treatment with nabiximols (n = 39 patients) was 25 days (range: 2 - 579 days) while the mean duration of treatment with oro-mucosal THC spray (n = 4 patients) was 151.5 days (range: 4 - 657 days). The average number of sprays/day for nabiximols during the last seven days of dosing was 5.4 ±3.28 vs. 14.5 ±16.84 for THC only. No dose escalation was noted in patients taking nabiximols beyond six months and up to one year following treatment initiation (509). Although the study was a non-comparative, open-label study with no formal hypothesis testing and mostly used descriptive statistics, a decrease from baseline in mean score on the BPI-SF (Brief Pain Inventory Short-Form) was observed for both "pain severity" and "worst pain" over the five weeks of treatment (509). However, the authors noted that the clinical investigators considered that their patients' pain control was sub-optimal. A negative change from baseline (i.e. indicating a worsening) was also reported in the physical functioning score on the EORTC QLQ-30 (an assessment tool to measure the quality of life of patients with cancer), although some improvements in scores for sleep and pain, between baseline and week 5 of treatment, were reported (509). Eight percent of the patients on nabiximols developed a serious nabiximols-associated adverse event. The most commonly reported adverse events for nabiximols were nausea/vomiting, dry mouth, dizziness, somnolence, and confusion (509).

In contrast to the above-mentioned studies using nabiximols, a randomized, double-blind, placebo-controlled, parallel group clinical trial of opioid-treated cancer patients with intractable chronic cancer pain (e.g. bone, mixed, neuropathic, somatic, visceral) reported no statistically significant difference between placebo and the nabiximols treatment group in the primary endpoint of 30% relief from baseline pain at study end (349). However, when using a continuous responder rate analysis as a secondary endpoint (i.e. comparing the proportion of active drug vs. placebo responders across the full spectrum of response from 0 to 100%), the study was able to report a statistically significant treatment effect in favour of nabiximols. Patients were taking median opioid equivalent doses ranging between 120 and 180 mg/day. Adverse events were dose-related, with only the highest dose group comparing unfavourably to placebo. The authors noted that the trial was a dose-ranging study, and that confirmatory studies are strongly warranted. The study design also did not permit the evaluation of a therapeutic index.

In Canada, nabiximols (Sativex®) is approved (with conditions) as an adjunctive analgesic in adults with advanced cancer who experience moderate to severe pain during the highest tolerated dose of strong opioid therapy for persistent background pain (290). Current dosing recommendations for nabiximols suggest a maximum daily dose of 12 sprays (32.4 mg THC and 30 mg CBD) over a 24 h period (107,112,290), although higher numbers of sprays/day have been used or documented in clinical studies (290,349). It should be noted that increases in the number of sprays/day were accompanied by increases in the incidence of adverse effects.

While there are no clinical trials of smoked marihuana for the treatment of cancer pain, the current Marihuana Medical Access Regulations (MMAR) allow the use of dried marihuana in cancer patients who experience severe pain and who have either not benefited from, or would not be considered to benefit from, conventional treatments (384).

"Opioid-sparing" effects and cannabinoid-opioid synergy

The "opioid-sparing" effect refers to the ability of a non-opioid medication to confer adjunctive analgesia with the use of a lower dose of the opioid thereby decreasing opioid-associated side effects. While there are some pre-clinical data supporting such an effect for cannabinoids, this is less well-established in published clinical studies. The following information summarizes the results from pre-clinical and clinical studies investigating cannabinoid-opioid interactions and the potential "opioid-sparing effect" of cannabinoids.

Pre-clinical data

There is a fair amount of evidence to suggest a functional interaction between the cannabinoid and the opioid systems, although much additional research is needed to understand precisely how the two systems communicate with one another. The evidence supporting a putative interaction between the cannabinoid and opioid systems comes from a number of observations. First, it is known that cannabinoids and opioids produce similar biological effects such as hypothermia, sedation, hypotension, inhibition of gastrointestinal motility, inhibition of locomotor activity, and anti-nociception (510,511,512). Furthermore, neuroanatomical studies in animals have demonstrated overlapping tissue distribution of the cannabinoid and opioid receptors, with both receptor types found in nervous system tissues associated with the processing of painful stimuli, namely the periaqueductal gray, raphe nuclei, and central-medial thalamic nuclei (510,511,512). There is also some evidence that the CB_1 and mu-opioid receptors can co-localize in some of the same neuronal sub-populations such as those located in the superficial dorsal horn of the spinal cord (510). This co-localization may play an important role in spinal-level modulation of peripheral nociceptive inputs (510). Both receptors also share similar signal transduction molecules and pathways, the activation of which generally results in the inhibition of neurotransmitter release (510,512). The role of these receptors in inhibiting neurotransmitter release is further supported by their strategic localization on pre-synaptic membranes (510). Evidence from some pre-clinical studies also suggests that acute administration of cannabinoid receptor agonists can lead to endogenous opioid peptide release, and that chronic THC administration increases endogenous opioid precursor gene expression (e.g. preproenkephalin, prodynorphin, and proopiomelanocortin) in different spinal and supraspinal structures involved in the perception of pain (510). A few studies have even demonstrated the existence of cannabinoid-opioid receptor heteromers, although the exact biological significance of such receptor heteromerization remains to be fully elucidated (513,514). Taken together, these findings suggest the existence of cross-talk between the cannabinoid and opioid systems. Furthermore, pre-clinical studies using a combination of different opioids (morphine, codeine) and cannabinoids (THC), at acute or sub-effective doses, have reported additive and even synergistic analgesic effects (515,516,517,518,519,520).

Clinical data
A limited number of clinical trials have been carried out to date with mixed results. One double-blind, placebo-controlled, crossover study of healthy human volunteers given low doses of THC, morphine, or a combination of the two drugs failed to find any differences between subjects' ratings of *sensory* responses to a painful thermal stimulus (521). However, the study did report that the combination of morphine and THC was associated with a decrease in the subjects' *affective* response to the painful thermal stimulus (521). The authors suggested that morphine and THC could combine to yield a synergistic analgesic response to the *affective* aspect of an experimentally-evoked pain stimulus. One clinical study (502) reported that patients suffering from chronic non-cancer pain and not responding to opioids experienced increased analgesia, decreased pain intensity, and decreased evoked pain when given either 10 or 20 mg dronabinol (for additional details see section 4.6.2.2, under "Clinical Studies With Orally Administered Prescription Cannabinoids"). More recently it was reported that patients suffering from chronic pain of various etiologies, unrelieved by stable doses of opioids (extended release morphine or oxycodone), experienced a statistically significant improvement in pain relief (27%, Confidence Interval = 9 - 46) following inhalation of vapourized cannabis (0.9 g, 3.56% THC, three times per day for five days) (187) (for additional details see section 4.6.2.2, under "Clinical Studies With Smoked or Vapourized Cannabis"). The findings from this study suggest that addition of cannabinoids (in this case inhaled vapourized cannabis) to existing opioid therapy for pain may serve to enhance opioid-associated analgesia (187).

In contrast, another study did not note a statistically significant decrease in the amounts of background or breakthrough opioid medications consumed by the majority of patients suffering from intractable cancer-related pain and taking either nabiximols or THC (112). Similarly, no statistically significant changes were observed in the amounts of background or breakthrough opioid doses taken by patients suffering from intractable cancer-related pain who were administered nabiximols (349). However, the design of the latter study did not allow proper assessment of an "opioid-sparing effect" of nabiximols.

In summary, while "cannabinoid-opioid synergy" has been proposed as a way to significantly increase the analgesic effects of opioids while avoiding, or minimizing, tolerance to the effects of opioid analgesics and circumventing, or attenuating, the well-known undesirable side effects associated with the use of either cannabinoids or opioids, the clinical results are mixed and further study is required on this topic (510,512).

4.6.2.4 Headache and Migraine

While historical and anecdotal evidence suggest a role for cannabis in the treatment of headache and migraine (522), no controlled clinical studies of cannabis or prescription cannabinoids to treat headache or migraine have been carried out to date (523,524).

With regard to migraine, an endocannabinoid deficiency has been postulated to underlie the pathophysiology of this disorder (525); however, the evidence supporting this hypothesis is limited. Clinical studies suggest that the concentrations of anandamide are decreased in the cerebrospinal fluid of migraineurs, while the levels of calcitonin-gene-related-peptide and nitric oxide (normally inhibited by anandamide and implicated in triggering migraine) are increased (526,527). In addition, the activity of the anandamide-degrading enzyme FAAH is significantly decreased in chronic migraineurs compared to controls (528).

In one case-report, a patient suffering from pseudotumour cerebri and chronic headache reported significant pain relief after smoking cannabis (529). In another case-report, a patient complaining of cluster headaches refractory to multiple acute and preventive medications reported improvement with smoked cannabis or dronabinol (5 mg) (530). However, these single-patient case-studies should be interpreted with caution. A recent report indicated that cannabis use was very frequent among a population of French patients with episodic or chronic cluster headache, and of those patients who used cannabis to treat their headache, the majority reported variable, uncertain, or even negative effects of cannabis smoking on cluster headache (531). It should also be noted that cannabis use has been associated with reversible cerebral vasoconstriction syndrome and severe headache (532). In addition, headache is an observed adverse effect associated with the use of cannabis or prescription cannabinoid medications (172,174,290,332,430,449), and headache is also one of the most frequently reported physical symptoms associated with cannabis withdrawal (533). It is therefore possible that using cannabis simply relieves headache caused by cannabis withdrawal.

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 four weeks of treatment (353). However, no significant changes in the number of tender points or tender point pain thresholds were observed (note: the use of the "tender point" as a diagnostic criterion for fibromyalgia is no longer an absolute requirement) (546). Patients were taking concomitant pain medications such as non-steroidal anti-inflammatory drugs, opioids, anti-depressants, and muscle relaxants. Nabilone did not have any lasting benefit in subjects when treatment was discontinued. A two-week randomized, double-blind, active-control, crossover study of 29 patients suffering from fibromyalgia reported that nabilone (0.5 - 1.0 mg before bedtime) improved sleep in this patient population (354).

The recently published Canadian Clinical Guidelines for the Diagnosis and Management of Fibromyalgia Syndrome (endorsed by the Canadian Pain Society and the Canadian Rheumatology Association) indicate that with regards to possible treatments, a trial of a prescribed pharmacologic cannabinoid may be considered in a patient with fibromyalgia, particularly in the setting of important sleep disturbance (this recommendation was based on Level 3, Grade C evidence) (506). For additional information regarding the use of cannabis/cannabinoids to alleviate sleep disorders or disturbances, please consult section 4.8.5.2.

4.7.4 Osteoporosis

Osteoporosis is a disease characterized by reduced bone mineral density and an increased risk of fragility fractures (547). It occurs when the normal cycle of bone remodelling is perturbed, leading to a net decrease in bone deposition and a net increase in bone resorption (548). While increasing evidence suggests a role for the endocannabinoid system in bone homeostasis, the role of cannabinoids in the treatment of osteoporosis has only been studied pre-clinically and the information remains unclear due to the complex and conflicting results among the various pre-clinical studies.

Pre-clinical studies

CB_1 and CB_2 receptors have been detected in mouse osteoblasts and osteoclasts, although CB_1 is expressed at very low levels compared to CB_2 (18,549,550). In fact, it appears that CB_1 receptors are expressed more abundantly in skeletal sympathetic nerve terminals in close proximity to osteoblasts (551). Besides the receptors, the endocannabinoids 2-arachidonoylglycerol (2-AG) and anandamide have been detected in mouse trabecular bone and in cultures of mouse osteoblasts and human osteoclasts (550,552,553). Taken together, these findings suggest the existence of a functional endocannabinoid system in bone.

The role of the endocannabinoid system in bone physiology has been investigated using mice carrying genetic deletions of either the CB_1 (*CNR1*) or CB_2 (*CNR2*) receptor genes. The skeletal phenotypes of CB_1 receptor knockout mice appear to vary depending on the gene targeting strategy used, the mouse strain, gender, time points at which the phenotypes were assessed, and the different experimental methodologies used to measure bone density (18). In one CB_1-deficient mouse strain, young female mice had normal trabecular bone with slight cortical expansion whereas young male mice had high bone mass (549,551). Loss of CB_1 receptor function was associated with protection from ovariectomy-induced bone loss (549). In addition, antagonism of CB_1 and CB_2 receptors prevented ovariectomy-induced bone loss *in vivo* (549). A subsequent study by the same group reported that CB_1 knockout mice had increased peak bone mass but eventually developed age-related osteoporosis (547). The increased peak bone mass was attributed to a reduction in osteoclast formation and activity, with preservation of normal osteoblast activity. In contrast, age-related bone loss in the knockout mice appeared to be caused by preferential formation and accumulation of adipocytes at the expense of osteoblasts within the bone-marrow space as well as decreased bone formation (547). In contrast to these studies, another study using a different gene targeting strategy and mouse strain reported that both male and female CB_1 knockout mice exhibited low bone mass, increased numbers of osteoclasts, and a decrease in the rate of bone formation (551). The effects of ovariectomy in this mouse line were not examined, most likely because the baseline bone mass was too small to properly measure differences between mice subjected to ovariectomy and controls.

The skeletal phenotypes of CB_2 receptor knockout mice have also been investigated. Ofek reported that CB_2-deficient mice display a low bone mass phenotype as well as age-related trabecular bone loss (554). These deficits were associated with increased numbers of osteoclasts and decreased numbers of osteoblast precursors (554). Furthermore, a selective CB_2 receptor agonist was reported to increase osteoblast proliferation and activity and to decrease the formation of osteoclast-like cells *in vitro*, and administration of this agonist attenuated ovariectomy-induced bone loss *in vivo* (554). While a more recent study supported the finding of age-related bone

loss, it failed to find any significant differences in peak bone mass between wild-type and knockout mice (555). Furthermore, and in contrast to the study by Ofek (554), selective stimulation of the CB_2 receptor was associated with an increase in osteoblast differentiation and function rather than proliferation. Another study reported no differences in peak bone mass between CB_2 receptor knockout mice and wild-type mice under normal conditions (556). Age-related bone loss was not measured in this study. Genetic ablation of the CB_2 receptor appeared to protect against ovariectomy-induced bone loss, an effect mimicked by administration of a CB_2-selective antagonist (556). Conversely, results from *in vitro* studies suggested that CB_2-selective agonists significantly increased osteoclast formation and osteoclast size (556). It may be relevant to note here that single nucleotide polymorphisms (SNPs) and SNP haplotypes located in the coding region of the CB_2 receptor gene have also been associated with osteoporosis in humans (557,558,559).

A pre-clinical study in rats measuring the impact of cannabis smoke on bone healing around titanium implants reported that chronic exposure to cannabis smoke reduced cancellous bone healing around the implants by reducing bone filling and bone-to-implant contact inside the implant threads (263). No such effect was observed for cortical bone (263).

4.8 Other diseases and symptoms

4.8.1 Movement disorders

The individual components of the endocannabinoid system are particularly abundant in areas of the brain which control movement, such as the basal ganglia (560). Motor effects generally arise as a consequence of changes in endocannabinoid system activity, with activation of the CB_1 receptor typically resulting in inhibition of movement (560). A number of studies have reported changes in CB_1 receptor levels and CB_1 receptor activity in motor diseases such as Parkinson's and Huntington's disease (561,562,563,564), and the findings from such studies suggest a role for the endocannabinoid system in the pathophysiology of these and other neurological diseases.

4.8.1.1 Dystonia

Pre-clinical data

A pre-clinical study in a hamster model of primary generalized dystonia reported a dose-dependent decrease in disease severity with administration of the synthetic CB_1 and CB_2 cannabinoid receptor agonist WIN 55,212-2 (565). However, anti-dystonic doses of the agonist were associated with severe side effects including depression of spontaneous locomotor activity and catalepsy. In addition, this CB receptor agonist increased the anti-dystonic effect of diazepam (565). A follow-up study by the same group confirmed the anti-dystonic efficacy of WIN 55,212-2 and also showed that cannabidiol delayed the progression of dystonia, but only at a very high dose (566). A pre-clinical study of anti-psychotic-induced acute dystonia and tardive dyskinesia in monkeys showed that oral dyskinesia, but not dystonia, was dose-dependently reduced by the synthetic CB_1 receptor agonist CP 55,940 (567).

Clinical data

While anecdotal reports suggest cannabis may alleviate symptoms associated with dystonia in humans (568), no properly controlled clinical studies of cannabis to treat dystonia have been published. A placebo-controlled, single-dose trial with 5 mg of Δ^9-THC administered to a musician with focal dystonia ("Musician's Dystonia") reported an improvement in motor control in the subject's affected hand, with tiredness and poor concentration cited as side effects associated with the use of Δ^9-THC (569). The therapeutic effect persisted until 2 h after intake, with a progressive return to baseline values after 5 h (569). A six-week, open-label, pilot trial of five patients taking 100 - 600 mg/day of cannabidiol reported modest dose-related improvements in all study subjects, but a worsening of tremor and hypokinesia in two patients with co-existing Parkinson's disease (570). Results of a double-blind, randomized, placebo-controlled study of 15 patients taking a single 0.03 mg/kg dose of nabilone and not taking any other anti-dystonia medication showed no significant reduction in dystonia (571).

4.8.1.2 Huntington's disease

Pre-clinical and human experimental data

Results from studies carried out in animal models of Huntington's disease (HD) as well as post-mortem studies carried out in HD patients suggest that brain CB_1 receptors, especially those found in the basal ganglia, are downregulated and/or desensitized as a result of the expression of the mutant Huntingtin protein, and that this occurs early in the course of the disease and prior to the appearance of overt clinical symptoms (561,572,573,574,575,576,577,578,579,580,581). A recent *in vivo* PET study of HD patients supports these findings, demonstrating profound decreases in CB_1 receptor availability throughout the gray matter of the cerebrum, cerebellum, and brainstem of HD patients even in early stages of the disease (582). Additional pre-clinical and post-mortem studies in HD patients indicate that the decrease in CB_1 receptor levels appears to be accompanied by an increase in CB_2 receptor levels in glial elements, astrocytes, and in reactive microglial cells (577,583). Thus, a significant amount of pre-clinical evidence and some limited clinical evidence suggests that changes in the endocannabinoid system are tightly linked to the pathophysiology of HD (577,580,581,582).

One pre-clinical study in a mouse model of HD reported no beneficial effects of Δ^9-THC (10 mg/kg/day) (584), while another study reported that Δ^9-THC (2 mg/kg/day) was associated with decreased pathology and delayed onset of HD-like symptoms compared to untreated HD mice (579).

Clinical data

With regard to clinical studies, one double-blind, placebo-controlled, 15-week, crossover trial of 15 patients with HD taking 10 mg/kg/day of oral cannabidiol did not report improvement in symptoms associated with HD (585). A randomized, double-blind, placebo-controlled, crossover pilot study found little or no beneficial effect of nabilone over placebo in patients with HD (586). However, nabilone was well tolerated in this patient population and did not appear to exacerbate chorea or HD-associated psychosis, although some adverse effects such as drowsiness and forgetfulness were noted. Patients were concomitantly taking other HD medications. The results from single-patient case studies are mixed. In one study, daily doses of 1.5 mg nabilone increased choreatic movements (587), while in another case improved mood and decreased chorea were noted in a patient who had smoked cannabis and who then continued on 1 mg nabilone b.i.d. (588).

4.8.1.3 Parkinson's disease

Endocannabinoid ligands, their synthesizing and degrading enzymes, and cannabinoid-activated receptors are highly abundant in the basal ganglia, the brain structures primarily affected in Parkinson's disease (PD) (560). Newly diagnosed PD patients and those undergoing PD medication washout were reported to have more than double the level of anandamide in their cerebrospinal fluid compared to controls, and these results parallel those seen in animal models of PD where dopamine cell loss is accompanied by elevations in anandamide levels (589). In animal models of PD the levels of CB_1 receptors appear to be downregulated during the early, pre-symptomatic stages of the disease, but during the intermediate and advanced phases of the disease there is an increase in CB_1 receptor density and function and an increase in endocannabinoid levels (590,591). Together, these studies suggest a complex link between the pathophysiology of PD and changes in the endocannabinoid system.

Results from animal studies suggest cannabinoid receptor agonists induce hypokinesia and thus are reported to be unlikely as suitable first-line treatments for PD (560,592). On the other hand, cannabinoid-induced hypokinesia could be useful in attenuating the dyskinesia observed in PD patients on long-term levodopa treatment (592). Cannabinoids having mixed CB_1 antagonist/CB_2 agonist properties as well as anti-oxidant effects (such as THCV) may possibly hold some therapeutic potential, but much further research is required to determine whether the beneficial effects of THCV observed in animal models of PD can find applicability in humans (593).

Clinical data

The results of clinical trials examining the role of cannabinoids (cannabis, nabilone and a standardized oral cannabis extract) in the treatment of PD are mixed. One study involving five patients suffering from idiopathic PD found no improvement in tremor after a single episode of smoking cannabis (1 g cigarette containing 2.9% Δ^9-THC, 29 mg total available Δ^9-THC), whereas all subjects benefited from the

administration of levodopa and apomorphine (594). A small randomized clinical trial of the synthetic cannabinoid nabilone (0.03 mg/kg) in seven patients with PD found that the treatment reduced levodopa-induced dyskinesia (595). In contrast, a four-week, randomized double-blind, crossover study demonstrated that an oral cannabis extract (2.5 mg Δ^9-THC and 1.25 mg cannabidiol per capsule, b.i.d.; maximum daily dose 0.25 mg/kg Δ^9-THC) did not produce any pro- or anti-parkinsonian action (596).

4.8.1.4 Tourette's syndrome

Anecdotal and case-reports have suggested amelioration of symptoms associated with Tourette's syndrome when smoking cannabis (597,598). A two-day, randomized, double-blind, placebo-controlled, crossover trial of single oral doses of Δ^9-THC (5, 7.5, or 10 mg) in 12 adult patients with Tourette's syndrome 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 (e.g. headache, nausea, ataxia, fatigue, anxiety) were noted in five patients (599). In contrast to healthy cannabis users, neither a 5 mg nor a 10 mg dose of Δ^9-THC caused cognitive impairment in patients with Tourette's syndrome (599). This study was followed up by a six-week, randomized, double-blind, placebo-controlled trial by the same research group. The authors 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 Δ^9-THC (600). The major limitations of all three clinical studies were their small sample size and their relatively short duration.

A Cochrane Collaboration Review examining the efficacy and safety of cannabinoids in treating tics, premonitory urges, and obsessive compulsive symptoms in patients with Tourette's syndrome concluded that there was insufficient evidence to support the use of cannabinoids in treating tics and obsessive compulsive behaviour in persons suffering from Tourette's syndrome (601).

4.8.2 Glaucoma

Glaucoma is a multi-factorial disease characterized by the progressive degeneration of the optic nerve and the death of retinal ganglion cells (RGC) ultimately leading to irreversible blindness (602). Increased intra-ocular 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 (265,602,603,604). 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 (605).

Ocular (as well as systemic) administration of cannabinoids typically lowers IOP by up to 30% (see (265) 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 (606,607,608,609,610).

A well-controlled pilot study of six patients with ocular hypertension or early primary open-angle glaucoma reported that single sub-lingual doses of 5 mg Δ^9-THC (applied by means of an oro-mucosal spray) significantly but temporarily reduced IOP 2 h after administration (264). A single sub-lingual dose of 20 mg cannabidiol (CBD) (containing ~ 1 mg Δ^9-THC) had no effect, while a single sub-lingual dose 40 mg of CBD (containing ~ 2 mg Δ^9-THC) caused a significant transient increase in IOP 4 h after administration (264). A non-randomized, unmasked, uncontrolled clinical study reported some improvement in IOP after oral ingestion of Δ^9-THC (2.5 or 5 mg q.i.d., up to a maximum of 20 mg/day; treatment duration range 3 - 36 weeks) in patients with end-stage, open-angle glaucoma not responsive to medications or surgery (611). Some patients appeared to develop tolerance to the intra-ocular pressure-lowering effects of Δ^9-THC, and almost half discontinued treatment due to Δ^9-THC-associated toxicity (e.g. dizziness, dry mouth, sleepiness, depression, confusion) (611). Aside from lowering IOP, cannabinoids such as Δ^9-THC and CBD may also have neuroprotective effects which could also be useful in the management of glaucoma (265,612,613,614,615,616,617,618,619,620,621). Results from a survey carried out among 1 516 glaucoma patients at tertiary glaucoma clinics in Toronto and Montreal suggested that approximately 13% of these patients claimed they used complementary and alternative medicines to treat glaucoma, and from among these patients 2.3% reported using cannabis to treat their glaucoma (622).

In conclusion, while smoking or eating cannabis has been shown to reduce IOP (623,624,625), cannabinoid-based therapy appears to be limited by the short duration of cannabinoid action (3 - 4 h) and unwanted physical and psychotropic effects.

4.8.3 Asthma

There is some historical and anecdotal evidence for cannabis as a treatment for asthma (626). In terms of pre-clinical data, there is some evidence suggesting a role for the endocannabinoid system in regulating bronchial smooth muscle tone (627) and studies in animals with classical and synthetic cannabinoids suggest a possible role for cannabinoid-based compounds in the treatment of asthma (628,629,630).

Early clinical studies demonstrated significant decreases in airway resistance and increases in specific airway conductance in healthy, habitual cannabis smokers shortly after smoking cannabis (631,632). This effect has been largely attributed to the bronchodilatory properties of Δ^9-THC (633). However, for asthmatics, the benefits of smoking cannabis are likely to be minimal. While smoking cannabis appears to decrease bronchospasm, increase bronchodilatation, and modestly improve respiratory function in some asthmatics in the short-term (634,635,636), cannabis smoke contains noxious gases and particulates that irritate and damage the respiratory system (633); hence, it is not a viable long-term therapy for asthma. Nevertheless, alternate methods of Δ^9-THC delivery by aerosol or oral administration have been studied. Doses of 100 and 200 µg of aerosolized Δ^9-THC significantly improved ventilatory function in asthmatics and were generally well tolerated (637,638). In another study, 5 - 20 mg of aerosolized Δ^9-THC rapidly and effectively increased airway conductance in healthy subjects, but caused either bronchodilatation or bronchoconstriction in asthmatics (639). Oral administration of 10 mg Δ^9-THC or 2 mg nabilone did not produce clinically significant bronchodilatation in patients with reversible airways obstruction (626,640,641).

4.8.4 Hypertension

CB_1 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 (642)).
There are very few studies on the effects of cannabis or cannabinoids on hypertension. In one early study, inhalation of cannabis smoke from cigarettes containing 2.8% Δ^9-THC caused a greater and longer-lasting decrease of arterial blood pressure in hypertensive subjects compared to normotensives (643). In one case-report, a woman with longstanding idiopathic intra-cranial hypertension reported improvement in her symptoms after smoking cannabis or after treatment with dronabinol (10 mg b.i.d initially, then 5 mg b.i.d.).

There are no reports on the use of low-dose cannabinoids as supplementary therapy in hypertension.

4.8.5 Psychiatric disorders

There are anecdotal and, in some cases, historical claims regarding the beneficial effects of cannabis and cannabinoids in the treatment of a variety of psychiatric disorders including anxiety, depression, sleep disorders, post-traumatic stress disorder, and withdrawal symptoms associated with drug abuse/addiction. The following sections provide information gathered from the scientific and medical literature regarding the use of cannabis and cannabinoids in the treatment of such disorders.

4.8.5.1 Anxiety and depression

Long-term cannabis users report reductions in anxiety, increased relaxation, and relief from tension (147). One survey conducted among over 4 400 respondents suggested that those who consumed cannabis daily or weekly reported a decrease in depressed mood, and an increase in positive affect, compared to respondents who claimed they never consumed cannabis (644). However, the study suffered from a number of serious drawbacks and should be interpreted with this in mind.

Pre-clinical and clinical evidence indicates important roles for the endocannabinoid system in both anxiety and depression. Results from animal studies suggest low doses of CB_1 receptor agonists reduce anxiety-like behaviour and increase anti-depressant-like responses (645,646). CB_1 receptor agonists appear to enhance central serotonergic and noradrenergic neurotransmission similar to the actions of anti-depressant medications (647,648). On the other hand, high-level stimulation of the CB_1 receptor, or administration of CB_1 receptor antagonists, reverse this response and can also trigger depression (155,647,649,650).

Suppression of endocannabinoid signalling is sufficient to induce a depressive-like state both in animals and in humans (reviewed in (651)). Furthermore, basal serum concentrations of both anandamide and 2-arachidonoylglycerol (2-AG) have been found to be significantly reduced in women with major depression (652). These findings suggest proper endocannabinoid tone plays an important role in regulating mood.

Clinical data for cannabis and THC

While the routine use of cannabis or prescription cannabinoid medications to treat primary anxiety or depression should be viewed with caution, and especially discouraged in patients with a history of psychotic disorders (see section 7.7.3.3), limited clinical evidence indicates that these drugs may present alternative therapeutic avenues in patients suffering from anxiety or depression secondary to certain chronic diseases. For example, in a study of HIV+ patients who reported using cannabis to manage their symptoms, 93% cited an improvement in anxiety and 86% cited an improvement in depression (653). It is important to note that 47% of those surveyed reported deterioration in memory. In another study of HIV+ cannabis smokers, high-dose dronabinol (5 mg q.i.d., for a total daily dose of 20 mg, for two days, followed by 10 mg q.i.d., for a total daily dose of 40 mg, for 14 days) was associated with an increase in self-reported "positive affect" (feeling "content"), but no change was observed in measures of anxiety or "negative affect") (193). The dosage employed in this study was eight times the recommended starting dose for appetite stimulation (i.e. 2.5 mg b.i.d), and double the maximal daily recommended dose. Improved mood was also reported as a beneficial effect of cannabis consumption in patients suffering from multiple sclerosis (654). Improvements in anxiety or depression were equally noted in a study of patients suffering from chronic neuropathic pain who smoked cannabis (172). It may be interesting to note here that rimonabant, a CB_1 receptor antagonist initially marketed as an anti-obesity medication, was withdrawn from the market because its use was associated with a significant incidence of anxiety, depression, and suicide, underscoring the role of the CB_1 receptor in regulating mood (650,655).

Cannabidiol

Increasing evidence suggests a role for cannabidiol (CBD) in decreasing anxiety, although the extent to which CBD (at the concentrations commonly found in cannabis) is able to achieve this effect remains uncertain (181,656). Pre-clinical studies have shown that CBD and CBD-derivatives decreased anxiety-like behaviour in a rat model of anxiety (657). An early clinical study showed that CBD (1 mg/kg) attenuated, but did not completely block, the anxiogenic effects of THC (0.5 mg/kg) in eight healthy volunteers with a history of marihuana use (97). A double-blind, crossover clinical study showed that a single dose of CBD (400 mg) significantly decreased anticipatory anxiety but increased mental sedation, although the findings were deemed to be preliminary and follow-up studies were suggested (658). Single-photon emission computed tomography (SPECT) brain imaging studies showed that in contrast to placebo, CBD decreased regional cerebral blood flow in the limbic and paralimbic cortical areas, regions implicated in the pathophysiology of anxiety (658). Furthermore, a randomized, double-blind, placebo-controlled study showed that 600 mg of CBD attenuated brain activity (blood oxygenation level-dependent response) in these cortical regions in response to anxiogenic stimuli (104). In contrast, 10 mg Δ^9-THC increased anxiety at baseline or in response to anxiogenic stimuli, but the brain regions affected by Δ^9-THC differed from those affected by CBD (104). A more recent double-blind, randomized, placebo-controlled clinical study showed that 600 mg of orally-administered CBD was associated with a significant reduction in anxiety, cognitive impairment, and discomfort in patients suffering from generalized social anxiety disorder subjected to a simulated public-speaking test (659). The authors caution that the study was preliminary in nature, with additional larger and well-controlled studies required to substantiate this effect. Although the precise mechanism by which CBD exerts its anxiolytic effects is not well established, it may act either by decreasing blood flow to brain regions associated with the processing of anxiety or fear-based stimuli (as mentioned above), or possibly through the modulation of serotonergic neurotransmission (660,661).

4.8.5.2 Sleep disorders

Pre-clinical data

There is some evidence to suggest a role for the endocannabinoid system in sleep. Subjects deprived of sleep for a 24 h period had increased levels of oleoylethanolamide (OEA), a natural analog of anandamide, in their cerebrospinal fluid but not in serum, whereas levels of anandamide were unchanged (662). In rats, both acute and sub-chronic administration of anandamide induces sleep (663). Cannabis and Δ^9-THC are known to have a number of effects on sleep. In general, it appears that these substances decrease sleep latency and are associated with greater ease in getting to sleep, but they consistently reduce total rapid-eye movement (REM) sleep and REM density (reviewed in (161)). Furthermore, due to the long half-life of THC, sedative effects typically persist into the day following cannabinoid administration (161).

Clinical data

A number of clinical studies point to a potential beneficial role for smoked cannabis or prescription cannabinoids (dronabinol, nabilone, nabiximols) in the treatment of sleep difficulties or disturbances associated with chronic pain (cancer pain, chronic non-cancer pain, diabetic peripheral neuropathy), HIV-associated anorexia-cachexia, multiple sclerosis, amyotrophic lateral sclerosis, spinal cord injury, rheumatoid arthritis, fibromyalgia, inflammatory bowel disease, multiple sclerosis-associated bladder dysfunction, post-traumatic stress disorder, and chemosensory alterations and anorexia-cachexia associated with advanced cancer (157,158,165,166,167,172,193,259,348,354,362,364,378,432,438,443,448,449,494,506). In most of these studies, the effect on sleep was measured as a secondary outcome. Although presented elsewhere throughout the text in the relevant sections, brief summaries of these studies are presented below.

Dronabinol

A four-week, randomized, double-blind, crossover pilot study of 19 patients suffering from amyotrophic lateral sclerosis (ALS) taking 2.5 - 10 mg per day of dronabinol reported improvements in sleep (443). Two studies reported that dronabinol (20 - 40 mg total Δ^9-THC/day) and smoked cannabis (~800 mg cigarettes containing 2 or 3.9% THC, administered four times per day for four days, corresponding to an estimated daily amount of 64 - 125 mg of Δ^9-THC) produced improvements in mood and sleep in patients with HIV/AIDS-associated anorexia-cachexia (166,167). A study of HIV+ cannabis smokers treated with dronabinol for 14 days (10 mg q.i.d., 40 mg daily) reported improvements in both objective and subjective measures of sleep, but only during the first eight days of the treatment regimen (193). A two-centre, phase II, randomized, double-blind, placebo-controlled 22-day pilot study carried out in adult patients suffering from chemosensory alterations and poor-appetite associated with advanced cancer of various etiologies reported statistically significant improvements in measures of quality of sleep and relaxation with dronabinol treatment (2.5 mg b.i.d.) compared to placebo (362).

Nabilone

An off-label, retrospective, descriptive study of 20 adult patients suffering from chronic non-cancer pain of various etiologies (post-operative or traumatic pain, reflex sympathetic dystrophy, arthritis, Crohn's disease, neuropathic pain, interstitial cystitis, HIV-associated myopathy, post-polio syndrome, idiopathic inguinal pain, chronic headaches) reported beneficial effects of nabilone (1 - 2 mg/day) on sleep (494). An enriched-enrolment, randomized-withdrawal, flexible-dose, double-blind, placebo-controlled, parallel assignment efficacy study of nabilone (1 - 4 mg/day), as an adjuvant in the treatment of diabetic peripheral neuropathic pain, reported statistically significant improvements in sleep and overall patient status (364). An open-label, non-placebo-controlled trial of nabilone for post-traumatic stress disorder reported that nabilone treatment was associated with an improvement in sleep time, cessation or lessening of nightmare severity, and cessation of night sweats (348). Dosing of nabilone was 0.5 mg, 1 h prior to bedtime; effective dose range was 0.2 mg - 4 mg nightly with all doses kept below 6 mg daily. A two-week, randomized, double-blind, active-control, crossover study of 29 patients suffering from fibromyalgia reported that nabilone (0.5 - 1.0 mg before bedtime) improved sleep in this patient population (354).

Smoked cannabis

Surveys carried out among patients suffering from multiple sclerosis reported cannabis-associated improvements in sleep in this patient population (164,165). Reported dosages of smoked cannabis varied from a few puffs, to 1 g or more, at a time (165). A cross-sectional survey of patients suffering from fibromyalgia reported that subjects claimed using cannabis (by smoking and/or eating) for a variety of symptoms associated with fibromyalgia, including sleep disturbance (158). A cross-sectional survey of 291

patients with inflammatory bowel disease (Crohn's disease or ulcerative colitis) reported that one of the reasons patients used cannabis was to improve sleep (157). A two-week, randomized, double-blind, placebo-controlled, cross-over study of patients suffering from chronic neuropathic pain reported that those who smoked 25 mg of cannabis containing 9.4% Δ^9-THC, three times per day for five days (2.35 mg total available Δ^9-THC per cigarette, or 7.05 mg total Δ^9-THC per day), fell asleep more easily and more quickly, and experienced fewer periods of wakefulness (172).

Orally administered prescription cannabinoid medications (Cannador and nabiximols)
A double-blind, placebo-controlled, phase III study, involving patients with stable multiple sclerosis (the **MU**ltiple **S**clerosis and **E**xtract of **C**annabis trial—i.e. "MUSEC") reported that a 12-week treatment with an oral cannabis extract ("Cannador") (2.5 mg Δ^9 –THC and 0.9 mg cannabidiol/dose) was associated with a statistically significant improvement in sleep compared to placebo (432). The majority of the patients using cannabis extract used total daily doses of 10, 15, or 25 mg of Δ^9–THC with corresponding doses of 3.6, 5.4, and 9 mg of CBD. Results from double-blind, crossover, placebo-controlled studies of oral Δ^9-THC and/or Δ^9-THC : CBD extract (nabiximols, marketed as Sativex®) suggested modest improvements in pain, spasticity, muscle spasms, and sleep quality in patients with spinal cord injury (378,448,449). A preliminary clinical study assessing the effectiveness of nabiximols (Sativex®) in pain caused by rheumatoid arthritis reported a modest, but statistically significant, analgesic effect and consequent improvement in quality of sleep (259). The mean daily dose in the final treatment week was 5.4 pump actuations (equivalent to 14.6 mg Δ^9-THC and 13.5 mg CBD). A sixteen-week, open-label pilot study of cannabis-based extracts (a course of Sativex® treatment followed by maintenance with 2.5 mg Δ^9-THC only) for bladder dysfunction in 15 patients with advanced multiple sclerosis reported significant decreases in nocturia and improvement in patient self-assessment of sleep quality (438).

The recently published Canadian Guidelines for the Diagnosis and Management of Fibromyalgia Syndrome (endorsed by the Canadian Pain Society and the Canadian Rheumatology Association) recommend that with regards to possible treatments, a trial of a prescribed pharmacologic cannabinoid may be considered in a patient with fibromyalgia, particularly in the setting of important sleep disturbance (this recommendation was based on Level 3, Grade C evidence) (506).

Data from withdrawal studies
Heavy cannabis users (mean number of joints smoked per week = 100) who abruptly discontinue cannabis use have been shown to exhibit changes in polysomnographic sleep measures, including lower total sleep times, less slow wave sleep, longer sleep onset, shorter REM latency, and worse sleep efficiency and continuity parameters compared to controls (664). Trouble getting to sleep, nightmares and/or strange dreams, and night sweats were frequently cited items associated with cannabis withdrawal (222). These sleep disturbances progress over the first two weeks of abstinence (665). Furthermore, sleep disturbances resulting from abrupt discontinuation of cannabis use may trigger users to relapse (274,665). The symptoms observed during abstinence from cannabis may alternatively reveal a pre-existing sleep disorder masked by the drug.

4.8.5.3 Post-traumatic stress disorder (PTSD)
Post-traumatic stress disorder (PTSD) refers to the development of a cluster of characteristic symptoms that follow exposure to an extreme traumatic stressor and which appears to involve aberrant memory processing and impaired adaptation to changed environmental conditions (666). Characteristic symptoms include persistent, intrusive recollections, or a re-experiencing of the original traumatic event (through dreams, nightmares, and dissociative flashbacks), numbing and avoidance, and increased arousal (348).

Role of the endocannabinoid system in PTSD
Increasing evidence suggests an important role for the endocannabinoid system in PTSD. The endocannabinoid system has been associated with the regulation of emotional states and cognitive processes, and neuroanatomical studies have detected the presence of endocannabinoid system elements in a number of brain structures involved in learning and memory, and in structures which also play central roles in fear conditioning and response (reviewed in (666)). Furthermore, similarities exist between the expression of fear and anxiety in humans suffering from phobias, PTSD, or other anxiety disorders, and the expression of conditioned fear in animals. Therefore, the use of certain animal behavioural models to study PTSD is feasible and relevant (666,667).

Pre-clinical data
A number of pre-clinical studies demonstrate that deletion of the CB_1 receptor or its inhibition by pharmacological antagonists prevent the extinction of aversive memories (i.e. learned inhibition of fear), a naturally adaptive process (667,668,669,670). Conversely, in some cases, CB_1 receptor agonism or increased endocannabinoid-mediated neurotransmission appear to enhance extinction to some degree (667,670), but further research is required to clarify and substantiate this effect. However, no studies have yet investigated the effects of Δ^9-THC *per se* on the extinction of aversive memories. Taken together, the evidence from pre-clinical studies suggests a role for the endocannabinoid system in the extinction of aversive memories, and raises the possibility that the endocannabinoid system may be a valid therapeutic target for the treatment of diseases associated with inappropriate retention of aversive memories or inadequate responses to aversive situations, such as PTSD or phobias (668).

Clinical data
Although anecdotal evidence suggests a role for cannabis in the management of PTSD symptoms, no properly controlled clinical trials on this topic exist. In fact the only clinical trial reported to date examining the effect of cannabinoids in PTSD is an open-label, non-placebo-controlled trial of nabilone for PTSD (348). Forty-seven patients diagnosed with PTSD (according to DSM-IV-TR criteria), having at least a two-year history of PTSD-related nightmares refractory to conventional therapies, a minimum of once weekly nightmares, and with no prior history of sensitivity to cannabinoids or evidence of psychotic reactions, were admitted into the study. Patients did not discontinue any concomitant psychotropic medications, and were started on 0.5 mg nabilone, 1 h prior to bedtime. All doses were kept below 6 mg daily. The effective dose range varied between 0.2 mg and 4 mg nightly. Seventy-two percent of patients self-reported total cessation or lessening of severity of nightmares (treatment duration 4 - 12 months or longer). Other self-reported benefits included an improvement in sleep time, a reduction in daytime flashbacks, and cessation of night sweats. Reported side effects included light-headedness, amnesia, dizziness, and headache. No tolerance to nabilone was observed in this clinical trial.

4.8.5.4 Alcohol and opioid withdrawal symptoms (drug withdrawal symptoms)

Alcohol
There is evidence to suggest complex functional interactions between ethanol and the endocannabinoid system (reviewed in (671)). Acute administration of ethanol in animals is associated with brain region-specific changes in endocannabinoid levels and in the expression of endocannabinoid system components (e.g. CB_1 receptor, FAAH) (671). Furthermore, modulation of endocannabinoid system components through genetic ablation of CB_1 receptor or FAAH expression, or by pharmacological inhibition of CB_1 receptor or FAAH activity, generally results in decreased ethanol consumption in animal models (although a few exceptions have been noted) (671). In contrast, activation of the CB_1 receptor appears to mediate the reinforcing properties of ethanol, facilitates ethanol consumption, and enhances re-instatement of ethanol self-administration in animal models (671). In the case of chronic ethanol consumption, the available evidence suggests long-term exposure to ethanol is in some cases associated with brain region-specific decreases in CB_1 receptor mRNA/protein expression and CB_1 receptor activity, as well as a decrease in FAAH expression and function (671). There is also some limited evidence gathered from animal studies that suggests the endocannabinoid system may be involved in the modulation of alcohol withdrawal symptoms, with CB_1 receptor agonism exacerbating withdrawal severity (671).

Opioids
Anecdotal information and findings from some animal studies suggest that cannabinoids might be useful in treating the symptoms associated with opioid withdrawal (512,672,673,674,675), but there are no supporting clinical studies in this regard. The overlapping neuroanatomical distribution, convergent neurochemical mechanisms, and comparable functional neurobiological properties of the cannabinoid and opioid systems may help explain why cannabinoids could substitute for opioids to potentially alleviate withdrawal symptoms associated with opioid abstinence (511). However, further research is required on this subject.

4.8.5.5 Schizophrenia and psychosis

The endocannabinoid system and psychotic disorders

There is increasing evidence implicating the endocannabinoid system in schizophrenia and psychosis (676). For example, levels of anandamide were reported to be significantly elevated in the cerebrospinal fluid and serum of patients with initial prodromal states of psychosis (677). In addition, anandamide levels were also elevated in the cerebrospinal fluid and serum of anti-psychotic-naïve patients with active schizophrenia (678,679). Post-mortem studies investigating CB_1 receptor densities in the brains of schizophrenic patients have also noted an upregulation of CB_1 receptor levels in the frontal and cingulate brain regions, areas of the brain typically afflicted in schizophrenia (676). While the precise role of the endocannabinoid system in psychosis and schizophrenia remains to be fully elucidated, it appears that such psychiatric disorders are accompanied by changes in the levels of endocannabinoids such as anandamide, as well as changes in CB_1 receptor expression level. Although it remains to be confirmed, one hypothesis holds that the endocannabinoid system may function as a feedback mechanism, negatively regulating dopamine release and dampening the hyperdopaminergic activity observed in the brains of schizophrenic subjects (676,680).

Substance use disorders and psychotic disorders

Interestingly, patients with severe mental illnesses such as schizophrenia are known to have high rates of substance use disorders, with cannabis being one of the substances most often used or misused by this population (681,682). Two competing hypotheses have tried to explain why patients with severe mental illnesses such as schizophrenia also have co-morbid substance abuse. The "self-medication" hypothesis, in the context of psychiatric disorders, posits that those who suffer from such disorders (e.g. schizophrenics) consume cannabis in order to alleviate specific psychopathological symptoms or alternatively to diminish the side effects resulting from the use of medications (682,683). While the "self-medication" hypothesis presents a compassionate, interesting, and attractive explanation to understand why schizophrenics have co-morbid substance abuse disorders, the hypothesis appears to have fallen out of favour (684). On the other hand, the "addiction-vulnerability" hypothesis claims that substance abuse vulnerability and schizophrenic symptoms share a common neuropathology (685). In other words, this hypothesis rests on the idea that certain pathological alterations in brain structure and function will predispose certain individuals to developing both schizophrenia and substance abuse disorders.

Cannabis/THC and psychosis

Regardless of which hypothesis is correct, there is much scientific evidence to suggest a positive association between cannabis use and the development of psychosis, especially in people susceptible to psychotic disorders but also in adolescents (138,139,141,143,144). Furthermore, controlled clinical studies carried out in those with no history of psychotic disorders reported the manifestation of transient schizophrenia-like symptoms induced by the intravenous administration of Δ^9-THC (140). Likewise, intravenous administration of Δ^9-THC in schizophrenics was associated with transient exacerbation of core psychotic symptoms (139).

Genetic factors

A number of studies have investigated the influence of potential genetic factors in the development of psychosis and schizophrenia, and more specifically as a function of interaction with cannabis use. Some studies have focused on the role of genetic polymorphisms at the catechol-O-methyltransferase gene (*COMT*) (686,687,688,689,690), and others have focused on polymorphisms at the *AKT1* gene (691,692,693). Taken together, the data from these studies strongly suggest that single-nucleotide polymorphisms at either the *COMT* or *AKT1* genes interact with cannabis use to predict the age at onset, as well as the likelihood of developing psychosis or schizophrenia in vulnerable individuals. Please consult section 7.7.3 for additional information on the adverse psychiatric effects associated with the use of cannabis and psychoactive cannabinoids (such as THC), and the role of genetic predisposition on the risk of developing a psychotic disorder. **The findings presented above and in section 7.7.3 suggest that cannabis use, as well as exposure to Δ^9-THC alone, would not be beneficial, and in fact would actually be harmful to those who may be suffering from psychotic disorders, or who may have a genetic predisposition or family history of psychosis or schizophrenia.**

Cannabidiol

A number of pre-clinical and clinical studies have suggested that, in contrast to THC, other cannabinoids such as cannabidiol (CBD) may in fact have anti-psychotic properties and may benefit psychotic patients (694,695). For example, studies in certain rat and mouse models of psychosis suggest that CBD (at doses of

15 - 60 mg/kg) reduces psychotic-like behavioural effects in a manner comparable to that observed with atypical anti-psychotic drugs (696,697). Furthermore, one clinical study showed that pre-treatment of a small number of human subjects with CBD (5 mg i.v.), but not placebo, diminished the emergence of psychotic symptoms 30 min after i.v. administration of Δ^9-THC (105). In contrast, a naturalistic study of cannabis users failed to show any differences in the prevalence of psychotic-like symptoms between subjects who reported smoking cannabis containing "low" or "high" levels of CBD; however the authors mention a number of confounding factors, including the lack of adjustment for alcohol consumption that could help explain this apparent inconsistency (656). An internet-based, cross-sectional study of 1 877 individuals who had a consistent history of cannabis use reported that individuals who had consumed cannabis with a higher CBD to THC ratio reported experiencing fewer psychotic episodes; however, the authors noted that the observed effects were subtle (113). Furthermore, the study was hampered by a number of important methodological issues suggesting the conclusions should be interpreted with caution. More recently, a four-week, double-blind, parallel-group, randomized, active-controlled clinical trial comparing CBD (200 mg, q.i.d., up to a total daily amount of 800 mg) to amilsupride (a dopamine D_2/D_3 receptor antagonist used in the treatment of schizophrenia) reported that both drugs were associated with a significant clinical improvement in symptoms with no significant difference between the two treatments (698). Treatment with CBD was well tolerated with significantly fewer side effects compared to those associated with anti-psychotic treatment (e.g. the presence of extra-pyramidal symptoms and lower prolactin release). In addition, CBD did not appear to significantly affect either hepatic or cardiac functions (698). Cannabidiol treatment, but not amilsupride, was also associated with an increase in serum levels of anandamide (698).

While there is some indication for a potential therapeutic role for CBD itself in the treatment of patients with pre-existing schizophrenia or psychosis or those who develop psychotic symptoms as a result of cannabis use, the extent to which CBD (at the levels typically found in cannabis) is able to ameliorate psychotic symptoms has not been firmly established and in fact, much of the cannabis consumed typically contains relatively low levels of CBD (60). For example, the CBD content of cannabis typically varies between 0.1 and 0.5%, although CBD levels of up to 8.8% (in hashish) have been noted (113). Therefore, a 1 g joint could contain between 1 mg (0.1%) and 88 mg (8.8%) of CBD—levels which are much lower than those usually administered in clinical trials (600 - 1500 mg/day) (699).

In conclusion, consumption of cannabis or other psychoactive cannabinoids (e.g. dronabinol, nabilone) should be treated with considerable caution in this patient population as these substances are believed to trigger psychotic episodes, lower the age of onset of symptoms, and contribute to a negative long-term prognosis in vulnerable individuals. Additionally, the therapeutic potential of CBD alone in the treatment of schizophrenia/psychosis, while promising, requires further study.

4.8.6 Alzheimer's disease and dementia

While still controversial, a widely accepted theory underlying the pathophysiology of Alzheimer's disease (AD) is the deposition of amyloid-β (Aβ) protein in specific brain regions leading to localized neuroinflammatory responses and accumulation of intra-cellular neurofibrillary tangles (composed of hyperphosphorylated tau protein); these events result in neuronal cell death with accompanying loss of functional synapses and changes in neurotransmitter levels (700). These pathological processes are thought to give rise to disease-associated symptoms such as memory deficits, and cognitive and motor impairments (700).

The endocannabinoid system and Alzheimer's disease

There is some evidence to suggest a role for the endocannabinoid system in the pathophysiology of AD (700,701). One *in vivo* study reported elevation in the levels of the endocannabinoid 2-arachidonoylglycerol (2-AG) in response to intra-cerebral administration of $A\beta_{1-42}$ peptide in animals (702). Another study using post-mortem brain samples from AD patients showed decreased anandamide levels with increasing $A\beta_{1-42}$ levels, but no association with $A\beta_{40}$ levels, amyloid plaque load, or tau protein phosphorylation (703).

Pre-clinical data

Pre-clinical studies suggest the endocannabinoid system protects against excitotoxicity, oxidative stress, and inflammation—all key pathological events associated with the development of AD (704). However, limited information exists regarding the use of cannabis or cannabinoids in the treatment of AD. Results from *in silico* and *in vitro* experiments suggest Δ^9-THC could bind and competitively inhibit acetylcholinesterase (AChE), which in the context of AD functions as a molecular chaperone accelerating the formation of amyloid fibrils and

forming stable complexes with Aβ (705). Δ^9-THC blocked the amyloidogenic effect of AChE, thereby diminishing Aβ aggregation (705). Other *in vitro* studies suggest that cannabidiol may have neuroprotective, anti-oxidant, and anti-apoptotic effects, as well as preventing tau protein hyperphosphorylation in cellular models of AD (706,707,708). Endocannabinoids have also been shown to prevent Aβ-induced lysosomal permeabilization and subsequent neuronal apoptosis *in vitro* (704). In pre-clinical animal models of AD, cannabidiol dose-dependently and significantly inhibited reactive gliosis and subsequent neuroinflammatory responses in Aβ-injected mice, at doses of 2.5 mg/kg/day and 10 mg/kg/day i.p., during a seven-day course of treatment (709). Another study using both *in vitro* and *in vivo* models of AD reported opposing roles for the CB_1 and CB_2 receptors in this context: CB_1 receptor agonism and CB_2 receptor antagonism were both associated with blunted Aβ-induced reactive astrogliosis and attenuation of neuroinflammatory marker expression (710).

Clinical data

There are very few clinical studies of cannabis or cannabinoids for the treatment of AD. One double-blind, placebo-controlled, six-week, crossover study of 12 patients suffering from Alzheimer-type dementia reported that 5 mg of dronabinol (Δ^9-THC) daily was associated with a decrease in disturbed behaviour (410). However, adverse reactions such as fatigue, somnolence, and euphoria (presumably unwanted) were reported in dronabinol-treated patients. One open-label pilot study of six patients suggested an evening dose of 2.5 mg dronabinol (Δ^9-THC) reduced nocturnal motor activity and agitation in those who were severely demented (711). In one case-report, a patient suffering from dementia of the Alzheimer-type who had been treated unsuccessfully with donepezil, memantine, gabapentin, trazodone, and citalopram was given nabilone (initially 0.5 mg at bedtime, and then twice per day) with immediate reduction in the severity of agitation and resistiveness and eventual improvement in various behavioural symptoms following six weeks of continuous treatment (712). It is unclear if the beneficial effects observed in these three studies are related to the non-specific sedative effects of Δ^9-THC or nabilone, or to a specific cannabinoid-dependent therapeutic mechanism of action. It is also worth noting that one cross-sectional study reported that prolonged use of ingested or inhaled cannabis was associated with poorer performance on various cognitive domains (e.g. information processing speed, working memory, executive function, and visuospatial perception) in patients with multiple sclerosis (178). Similar adverse effects of cannabis/cannabinoids on cognition could potentially apply in the context of Alzheimer-type dementia.

A Cochrane database systematic review of cannabinoids for the treatment of dementia concluded that there was insufficient clinical evidence to suggest cannabinoids as being effective in the improvement of disturbed behavior in dementia or in the treatment of other symptoms of dementia (713).

4.8.7 Inflammation

The role of the endocannabinoid system in inflammation is complex as the endocannabinoid system has been implicated in both pro- and anti-inflammatory processes (701). Endocannabinoids, such as anandamide and 2-arachidonoylglycerol (2-AG), are known to be produced and released by activated immune cells and to act as immune cell chemoattractants promoting or directing the inflammatory response (714). On the other hand, cannabinoids can also suppress the production of pro-inflammatory cytokines and chemokines and thus may have therapeutic applications in diseases with an underlying inflammatory component (714,715). For information on other diseases with an inflammatory component such as the arthritides or inflammatory bowel disease, please consult sections 4.7 and 4.8.8.2, respectively, of this document.

4.8.7.1 Inflammatory skin diseases (dermatitis, psoriasis, pruritus)

The skin possesses an endocannabinoid system (41). CB_1 and CB_2 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, sweat gland ducts, mast cells, and macrophages (716). The endocannabinoid system and certain associated signaling pathways (e.g. PPARγ, TRPV1) appear to regulate the balance between keratinocyte proliferation, differentiation, and apoptosis; together, these systems may play a role in cutaneous homeostasis but also in diseases such as psoriasis, which is characterized by keratinocyte proliferation and inflammation (41,717,718,719).

Pre-clinical and clinical studies

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 certain cannabinoids, while others suggest an antagonistic role (reviewed in (41)). In clinical studies, experimentally-induced histamine-triggered pruritus was reduced by peripheral administration of the potent synthetic CB_1/CB_2 cannabinoid receptor agonist HU-

210, and the accompanying increases in skin blood flow and neurogenic mediated flare responses were attenuated (720). In another study, topically applied HU-210 significantly reduced the perception of localized pain in human subjects following locally restricted application of capsaicin to the skin, and reduced subsequent heat hyperalgesia and touch-evoked allodynia without any psychomimetic effects (721). On the other hand, there have also been some case-reports of contact urticaria following exposure to cannabis flowers, and extreme sensitization to Δ^9-THC and cannabinol has also been documented in an animal model of contact dermatitis (722,723). Therefore, while it is possible that some cannabinoids (e.g. HU-210) may have therapeutic value in the treatment of certain inflammatory skin conditions (such as psoriasis, pruritus, and dermatitis), it is also possible for some cannabinoids to trigger adverse skin reactions. Much further research is required in this area.

4.8.8 Gastrointestinal system disorders (irritable bowel syndrome, inflammatory bowel disease, hepatitis, pancreatitis, metabolic syndrome/obesity)

Historical and anecdotal reports suggest that cannabis has been used to treat a variety of gastrointestinal disorders (e.g. diarrhea, inflammation, and pain of gastrointestinal origin) (724,725,726).

The endocannabinoid system and gastrointestinal disorders

The expression of both the CB_1 and CB_2 receptors has been detected in the enteric nervous system (enteric sensory neurons, nerve fibers and terminals), whereas the human colonic epithelium, colonic epithelial cells lines, and stomach parietal cells appear to only express the CB_1 receptor (28,29). CB_2 receptor expression appears to be upregulated in sections of the colon in patients with inflammatory bowel disease (31). In contrast, the expression and localization of endocannabinoid synthesizing enzymes have not been well determined (31). However, studies in animals indicate that the endocannabinoid degradative enzymes FAAH and MAGL can be found in the gastrointestinal tract (31). For example, FAAH is expressed in the stomach and in the large and small intestines, and has also been localized to the cell bodies of the myenteric plexus (31). MAGL expression has been detected in the muscle and mucosal layers of the duodenum and the ileum, as well as in the proximal and distal colon, and in the nerve cell bodies and nerve fibers of the enteric nervous system (727). There also appears to be some regional variation in the levels of endocannabinoids in the gut; 2-arachidonoylglycerol (2-AG) appears to be more abundant in the ileum than the colon, whereas the opposite is true of anandamide (31). CB_1 and CB_2 receptors appear to be expressed in the pancreas (30), whereas the CB_1, but not the CB_2 receptor, is expressed in the liver under normal conditions (32,33).

Cannabinoids appear to have many functions in the digestive system including the inhibition of gastric acid production, gastrointestinal motility, and secretion and ion transport, and the attenuation of visceral sensation and inflammation (reviewed in (31)). Perturbations in the levels of various components of the endocannabinoid system have been noted in experimental models of gastrointestinal disorders, as well as in clinical studies (reviewed in (31). The sections below summarize the information regarding the uses of cannabis and cannabinoids in the treatment of various disorders of the gastrointestinal system.

4.8.8.1 Irritable bowel syndrome

Irritable bowel syndrome (IBS) is the most common functional gastrointestinal disorder encountered in clinical medicine (728). It is a spectrum of disorders characterized by the presence of chronic abdominal pain and/or discomfort and alterations in bowel habits (728,729). Symptom patterns can be divided into diarrhea predominant (D-IBS), constipation predominant (C-IBS), and a mixed pattern (M-IBS) (729,730). While the pathophysiology of IBS remains unclear, the disorder is thought to be caused by dysregulation of the 'brain-gut axis' in response to psychological or environmental stressors or to physical stressors such as infection or inflammation, and is characterized by altered gut motility and visceral hypersensitivity (728,729). There is also some emerging evidence that suggests an association between genetic alterations in genes coding for certain endocannabinoid system proteins (e.g. *FAAH* and *CNR1*) and the pathophysiology of IBS (731,732,733).

Pre-clinical data

A few pre-clinical studies in animal models of IBS have been carried out to date. Two studies have employed mechanically-induced colorectal distension to trigger an acute visceral pain response in rodents as a model of IBS-associated visceral hypersensitivity. One study in rats showed that intra-peritoneal injection of different synthetic cannabinoid receptor agonists inhibited pain-related responses to experimentally-induced colorectal distension when administered *prior* to the experimental stimulus (734). Intravenous administration of

different synthetic cannabinoid receptor agonists also appeared to inhibit the overall pain-related responses to experimentally-induced colorectal distension in rats, as well as in mice, when administered *after* the experimental stimulus (735). In another study, subcutaneous administration of CB_1 or CB_2-selective agonists was reported to reduce the enhanced small intestinal transit observed in a mouse model of post-inflammatory IBS (736).

Clinical data with dronabinol

There are only a handful of clinical studies examining the effects of cannabinoids in human experimental models of IBS and in patients with IBS.

One double-blind, randomized, placebo-controlled, parallel-group study examined the effects of dronabinol on gastrointestinal transit, gastric volume, satiation, and post-prandial symptoms in a group of healthy volunteers (737). A 5 mg dose of dronabinol was associated with a significant delay in gastric emptying in female subjects, but not male subjects (737). No significant differences in either small bowel or colonic transit were observed between subjects administered dronabinol or placebo in any gender group (737). The 5 mg dose of dronabinol was used because a 7.5 mg dose caused intolerable side effects in more than half of the subjects (737). Adverse effects associated with the consumption of a 5 mg dose of dronabinol included dizziness/light-headedness, dry mouth, disturbed mental concentration, and nausea (737).

A subsequent double-blind, randomized, placebo-controlled, parallel-group study carried out by the same group investigated the effects of dronabinol on colonic sensory and motor functions of healthy human volunteers (738). Administration of a 7.5 mg dose of dronabinol significantly increased colonic compliance, especially in females, and reduced pre- and post-prandial phasic colonic motility and pressure (738). Colonic compliance is defined as the change in distensibility of the colon in response to a change in applied intracolonic pressure and it is used as a measure of colonic viscoelastic properties and as an indicator of colonic motor/contractile activity (738,739,740). Decreased compliance is typically associated with urgency and diarrhea, while increased compliance is typically associated with constipation (739,741). An increase in colonic compliance in this setting could indicate a return towards proper colonic function. In contrast to the results seen in the pre-clinical rodent studies, dronabinol increased the sensory rating of pain but did not affect the sensory rating of gas, or the thresholds for first sensation of either gas or pain during experimentally-induced random phasic distensions (738).

A double-blind, randomized, parallel-group study investigated the effects of escalating doses of dronabinol on colonic sensory and motor functions in a population of mostly female patients diagnosed with IBS according to Rome III criteria (IBS-C, IBS-D, or IBS-A (i.e. *alternating* between diarrhea and constipation)) (742). Only the highest dose of dronabinol tested (5 mg) was associated with a small, but statistically significant, increase in colonic compliance (742). Furthermore, the effect on colonic compliance appeared to be more pronounced in the IBS-D/A sub-group compared to IBS-C. No significant differences were observed on fasting or post-prandial colonic tone in response to dronabinol at any dose. However, the highest dose of dronabinol (5 mg) was associated with a significant reduction in the proximal left colon motility index, with a trend towards decreased colon motility indices (742). Treatment effects were significant on the proximal colon motility index in patients with IBS-D/A, but not in IBS-C, and only for the highest dose (742). Sensation thresholds and sensation scores for gas and pain during experimentally-induced ramp distensions did not differ significantly among the different treatment groups (742). The effects of genotype and dronabinol dose interaction on gas and pain sensation ratings, as well as on proximal fasting and distal fasting motility indices were also investigated. The results from these preliminary pharmacogenetic studies raise the possibility that the effects of dronabinol on colonic compliance and proximal colonic motility may be influenced by genetic variations in the *FAAH* and *CNR1* genes, but further studies are required to substantiate this hypothesis (742).

A subsequent double-blind, randomized, placebo-controlled, parallel-group study in a population of mostly female patients with IBS-D (Rome III criteria) further investigated gene-treatment interactions on colonic motility in this sub-set of IBS patients (743). Neither the 2.5 mg b.i.d. nor the 5 mg b.i.d. doses of dronabinol had any statistically significant effects on gastric, small bowel, or colonic transit (743). The effects on colonic transit were also examined as a function of genotype-by-treatment dose interaction. While treatment with dronabinol appeared to decrease colonic transit in subjects carrying the *CNR1* rs806378 CT/TT polymorphism, these effects were not statistically significant. Adverse effects were reported not to differ significantly between treatment groups.

4.8.8.2 Inflammatory bowel diseases (Crohn's disease, ulcerative colitis)

Inflammatory bowel diseases (IBD) include Crohn's disease and ulcerative colitis (744). Crohn's disease is characterized by patchy, intra-mural inflammation which may affect any part of the gastrointestinal tract (745). Symptoms include abdominal pain, diarrhea and weight loss as well as systemic symptoms of malaise, anorexia, and/or fever (745). Crohn's disease may cause intestinal obstruction due to strictures, fistulae, or abscesses (745). Ulcerative colitis is characterized by diffuse mucosal inflammation limited to the colon (745). Symptoms commonly include bloody diarrhea, colicky abdominal pain, urgency, or tenesmus (745). Both diseases are associated with an equivalent increased risk of colonic carcinoma (745).

The endocannabinoid system and IBD

Endocannabinoid system changes have been observed in the gastrointestinal tracts of experimental animal models of IBD, as well as in those of IBD patients (31,744). These changes include changes in the levels of endocannabinoids, cannabinoid receptors, and endocannabinoid synthesizing and degrading enzymes (28,31,744,746,747,748).

Pre-clinical data

Pre-clinical experiments in animal models of IBD suggest cannabinoids and endocannabinoids may limit intestinal inflammation and disease severity via activation of CB receptors (749,750,751,752,753,754).

Acute colitis

Mice bearing a genetic deletion of the CB_1 receptor had a stronger colonic inflammatory response (749) following rectal administration of dinitrobenzene sulfonic acid (DNBSA), an established method of inducing an acute colitis-like phenotype in mice (755). In contrast to wild-type mice, histological examination of the colons of CB_1 knockout mice treated with DNBSA revealed disruption of epithelial structure, with extensive hemorrhagic necrosis and neutrophil infiltration into the mucosa, and with acute inflammation extending into the sub-mucosa and muscle layer (749). Pharmacological blockade of the CB_1 receptor in wild-type mice produced similar effects accompanied by thickening of the bowel wall, inflammatory infiltrates, and an increase in lymphoid-follicle size associated with adherence to surrounding tissues (749). Furthermore, in contrast to CB_1 knockout mice, wild-type mice retained a significantly greater body weight following DNBSA treatment (749). Treatment of wild-type mice with the potent synthetic CB_1 and CB_2 receptor agonist HU-210, prior to and after DNBSA insult, significantly reduced the macroscopic colonic inflammatory response (749). Mice bearing a genetic deletion of the FAAH enzyme also displayed an attenuated inflammatory response to DNBSA compared to wild-type littermates (749).

An analogous study found that CB_1 and CB_2 receptor knockout mice and CB_1/CB_2 receptor double knockout mice showed increased extent of colonic inflammation, increased loss of crypt architecture, increased hyperemia/edema, and an increased degree of infiltration of inflammatory cells compared to wild-type mice following trinitrobenzene sulfonic acid (TNBSA)-induced acute colitis (753). All three knockout strains exhibited severe transmural colitis, with severe loss of epithelium, thickening of the bowel wall, and inflammatory infiltrates compared to wild-type mice (753). Genetic deletion of either or both CB receptors was also associated with significantly increased mRNA levels of various pro-inflammatory cytokines compared to wild-type mice in mice treated with TNBSA (753).

TNBSA-induced acute colitis in mice was associated with a significant upregulation of CB_2 receptor mRNA levels in the proximal and distal colons of treated mice (756). Intra-peritoneal administration of CB_2 receptor agonists, prior to and following TNBSA-induced colitis, was associated with a reduction in the macroscopic damage (e.g. reduced ulceration, reduction in colonic adhesions, and reduced colonic shortening) (756). Conversely, administration of a CB_2 receptor antagonist aggravated TNBSA-induced colitis (756).

Acute colitis and cannabidiol

Intra-peritoneal injection of cannabidiol (5 - 10 mg/kg) prior to DNBSA-induced acute colitis was associated with a significant attenuation of body weight loss caused by DNBSA (757). Cannabidiol (CBD) also reduced the wet weight/colon length ratio of inflamed colonic tissue, a marker of the severity and extent of the inflammatory response (757). Furthermore, CBD (5 - 10 mg/kg) significantly reduced macroscopic damage associated with DNBSA administration (mild edema, hyperemia, and small bowel adhesions) as well as microscopic damage (epithelium erosion, and mucosal and sub-mucosal infiltration of inflammatory cells

with edema) (757). Lastly, treatment with CBD significantly attenuated the observed increases in some biological markers associated with inflammation and oxidative stress, as well as attenuating the observed increases in the colonic levels of anandamide and 2-AG (757).

Another study reported that intra-peritoneal (10 mg/kg) or intra-rectal (20 mg/kg) pre-treatment with CBD, again administered *prior* to induction of colitis by TNBSA, caused a significant improvement of the colitis score and a decrease in the myeloperoxidase activity (a measure of neutrophil accumulation in colonic tissue) (758). No such differences were observed for orally administered CBD. Histological examination of colonic tissue further revealed decreased destruction of the epithelial lining, a reduction in colon thickness, and less infiltration of immunocytes compared to vehicle-treated mice (758). In contrast to the study by Borrelli (757), no differences in body weight were observed between vehicle-treated and CBD-treated mice that had developed colitis (758).

The effects of intra-peritoneal injections of THC, CBD, and a combination of THC and CBD on TNBSA-induced acute colitis in rats have been investigated (754). In one experiment, treatment with 10 mg/kg of THC alone, a combination of 5 mg/kg THC and 10 mg/kg CBD, a combination of 10 mg/kg THC and 10 mg/kg CBD, or sulfasalazine alone was associated with a statistically significant decrease in the macroscopic damage score (MDS) (754). The MDS is a linear scale measuring the extent of macroscopic damage to the colon and includes markers such as the presence or absence of hyperemia, ulceration, inflammation, adhesions, damage length, and diarrhea (754). Furthermore, treatment of rats (with experimentally-induced colitis) with CBD alone did not affect body weight. However, treatment with 5 or 20 mg/kg THC alone, or a combination of 10 mg/kg THC and 10 mg/kg CBD, resulted in a significant reduction of body weight gain in rats with experimentally-induced colitis in comparison with the vehicle group (754). Myeloperoxidase activity, a measure of inflammation, was significantly decreased in CBD-treated rats and in rats treated with 10 or 20 mg/kg THC, or 5 mg/kg THC and 10 mg/kg CBD (754). Treatment with 10 mg/kg CBD, 10 mg/kg THC, 10 mg/kg THC and 10 mg/kg CBD, or sulfasalazine alone was also associated with decreased disturbances in colonic motility resulting from TNBSA-induced colitis (754).

In a different experimental mouse model of acute colitis, the CB_1 receptor-selective agonist ACEA and the synthetic CB_2 receptor-selective agonist JWH-133, when injected intra-peritoneally prior to and after colonic insult, significantly reduced colon weight gain, colon shrinkage, colon inflammatory damage score, and diarrhea (751).

Inhibition of the 2-AG degrading enzyme monoacylglycerol lipase (MAGL) in mice by intra-peritoneal administration of a MAGL inhibitor *prior* to induction of acute colitis by TNBSA was associated with decreased macroscopic and histological colon alterations, as well as decreased colonic expression of pro-inflammatory cytokines (759). Inhibition of MAGL was also associated with a reduction in colitis-related systemic and central inflammation in the liver and the CNS (759). Co-administration of either CB_1 or CB_2 receptor-selective antagonists completely abolished the protective effect in the colon afforded by MAGL inhibition, and partially reversed the protective anti-inflammatory effects associated with MAGL inhibition in the liver (759).

Chronic colitis

Intra-peritoneal administration of the synthetic CB_2 receptor-specific agonist JWH-133 significantly attenuated colitis-associated body weight loss, inflammation, leukocyte infiltration, and tissue damage in a mouse model of spontaneous chronic colitis (760). This CB_2 receptor specific agonist also reduced T-cell proliferation, increased T-cell apoptosis, and increased the numbers of mucosal and systemic mast cells (760).

Ileitis

The effect of cannabichromene on inflammation-induced hypermotility in a mouse model of intestinal ileitis has been studied (761). Ileitis is characterized by disruption of the mucosa, infiltration of lymphocytes into the sub-mucosa, increased myeloperoxidase activity, and vascular permeability (761). Administration of cannabichromene (15 mg/kg i.p.) following croton oil-induced intestinal inflammation was associated with a decrease in the expression of CB_1 and CB_2 receptor mRNA in the jejunum, but not in the ileum (761). Cannabichromene did not affect upper gastrointestinal transit, colonic propulsion, or whole gut transit in untreated mice, but did reduce intestinal motility in croton oil-treated mice at 10 and 20 mg/kg i.p. (761). Cannabichromene also dose-dependently and significantly inhibited contractions induced by acetylcholine, as

inverse agonist attenuated this effect (805). In humans, intravenous injection of 6 mg of Δ^9-THC to healthy, non-obese male volunteers was associated with acute impairment of glucose tolerance in response to glucose challenge with no change in plasma insulin levels (806).

Survey data

A cross-sectional study of 10 896 adults, ages 20 - 59, who were participants in the National Health and Nutrition Examination Survey III (NHANES), a nationally representative sample of the U.S. population, reported that cannabis use was independently associated with a decreased prevalence of diabetes mellitus, and that cannabis users had lower odds of developing diabetes mellitus compared to non-users (807). The lowest prevalence of diabetes mellitus was seen in current, light cannabis users, but current heavy users and past users also had a lower prevalence of diabetes mellitus than non-cannabis users (807). Due to limitations in study methodology (e.g. cross-sectional nature of the study, self-report bias, and inconsistent sampling methodology) as well as the possibility of additional and uncontrolled confounding factors, the authors indicate that it is not yet possible to conclude that cannabis use does not lead to diabetes mellitus, nor that cannabis should be considered a treatment for this disorder (807).

Cannabis, the endocannabinoid system, and acute and chronic pancreatitis

Acute, heavy cannabis use has been linked to the development of acute pancreatitis (253,254,255,256). Acute pancreatitis is a potentially lethal disorder involving inflammation, cell death, and complex neuroimmune interactions; the management of chronic pancreatitis remains clinically challenging with no definite cure and supportive measures are the only treatment available (808,809). Pancreatic tissue isolated from patients with *acute* pancreatitis has been reported to have a marked upregulation of CB_1 and CB_2 receptors in the acini and ducts as well as elevated levels of the endocannabinoid anandamide but not 2-AG (808). In a subsequent study, an increase in the expression levels of CB_1 and CB_2 receptors, and a decrease in the levels of endocannabinoids (anandamide and 2-AG) were noted in tissue samples isolated from patients suffering from *chronic* pancreatitis compared to pancreatic tissues isolated from healthy subjects (809). In addition, in contrast to the findings obtained for acute pancreatitis (808), tissues isolated from patients with chronic pancreatitis appeared to have decreased levels of anandamide and 2-AG (809). Activation of CB_1 and CB_2 receptors in chronic pancreatitis-derived pancreatic stellate cells was also associated with the induction of a quiescent-cell phenotype as well as the downregulation of extracellular matrix protein production and inflammatory cytokine production (809).

Pre-clinical data and acute or chronic pancreatitis

There are only a handful of reports on the effects of cannabinoids in experimental animal models of acute or chronic pancreatitis, and the findings from these reports are conflicting. Thus, the use of cannabinoids in the treatment of acute or chronic pancreatitis remains unclear. Information gathered from pre-clinical animal studies is summarized below.

Elevations in the plasma levels of anandamide have been noted in a rat model of severe acute pancreatitis (810), and administration of the CB_1 receptor antagonist AM251 after induction of pancreatitis appeared to improve the course of the disease (810). In another study, administration of anandamide *prior* to induction of pancreatic damage further aggravated the usual course of the disease, whereas pre-treatment with the CB_1 receptor antagonist AM251 prevented the development of cerulein-induced pancreatitis and when administered *after* injury also appeared to reverse cerulein-induced pancreatic damage (811). Similarly, mice treated with the CB_1 receptor antagonist rimonabant *prior* to cerulein-induced pancreatitis exhibited significantly decreased pancreatic damage as well as decreased production of inflammatory cytokines (812). Subcutaneous administration of a synthetic CB_1/CB_2 receptor agonist, both prior to as well as after induction of acute pancreatitis in mice, attenuated the abdominal pain, inflammation, and tissue pathology associated with pancreatitis (808). In contrast, a different study reported that pre-treatment of rats with a synthetic CB_1/CB_2 receptor agonist *before* induction of experimentally-induced pancreatitis attenuated the extent of tissue damage and the release of inflammatory cytokines, whereas administration of the same agonist *after* the induction of pancreatitis had the opposite effects and appeared to aggravate the course of the disease (813). These contradictory findings may be due to differences in experimental methods, differences in timing of drug administration, differences in the types of agonists and antagonists that were used, differences in the route of administration, and differences in animal species.

4.8.9 Anti-neoplastic properties

A number of studies have implicated the endocannabinoid system in the pathophysiology of cancer. In general, endocannabinoids seem to have a protective effect against carcinogenesis, and proper regulation of local endocannabinoid tone is likely an important factor in controlling the malignancy of different cancers (814). When compared with healthy tissues, the levels of endocannabinoids appear to be elevated in glioblastomas, meningiomas, pituitary adenomas, prostate and colon carcinomas, and endometrial sarcomas (746,815,816,817,818,819). The expression levels of cannabinoid receptors are also differentially regulated in normal versus malignant cells, with increased or decreased levels of these receptors varying with cancer type (reviewed in (814)). Such differences in the levels of endocannabinoids and in the patterns of expression levels of cannabinoid receptors across different cancer types reflect the complex role of the endocannabinoid system in cancer and are likely to pose challenges to potential therapeutic approaches. Nonetheless, a number of pre-clinical studies have shown that endocannabinoids, certain synthetic cannabinoid agonists, and some phytocannabinoids can inhibit tumour growth and progression of numerous types of cancers through various mechanisms including promotion of apoptosis, cell-cycle arrest/growth inhibition, and prevention of metastasis through inhibition of tumour invasion, migration, and neo-angiogenesis (reviewed in (814,820)).

In general, the anti-neoplastic effects of Δ^9-THC appear to be biphasic: lower doses (under 100 nM), comparable to those typically seen in clinical or therapeutic settings, are considered pro-proliferative; higher doses (above 100 nM) are thought to be anti-proliferative (821), although exceptions have been noted. Furthermore, cannabinoid concentrations above 100 nM, that is two orders of magnitude above the average affinity of these receptors for cannabinoids, are likely to produce off-target, CB receptor-independent effects (822). As a point of reference, single oral doses of dronabinol (Δ^9-THC) of 2.5, 5, and 10 mg have been associated with mean peak Δ^9-THC plasma concentrations of 0.65, 1.83, and 6.22 ng/mL, respectively (174). These concentrations correspond to concentrations of 0.002, 0.006, and 0.02 µM (or 2, 6, and 20 nM) Δ^9-THC. Doubling of these daily oral doses is associated with mean peak Δ^9-THC plasma concentrations of 1.3, 2.9, and 7.9 ng/mL Δ^9-THC (174), respectively, corresponding to 0.004, 0.009, and 0.03 µM (or 4, 9, and 30 nM) Δ^9-THC. Continuous dosing for seven days with 20 mg doses of dronabinol (total daily doses of 40 - 120 mg dronabinol) gave mean plasma Δ^9-THC concentrations of ~20 ng/mL or ~0.06 µM (60 nM) Δ^9-THC (288). Smoking a 1 g joint containing 12.5% Δ^9-THC can be assumed, based on the literature, to yield peak plasma Δ^9-THC concentrations between 50 and 100 ng/mL or more (see section 3.1 "Smoking", subsection "Plasma concentrations of Δ^9-THC following smoking"). Such Δ^9-THC plasma concentrations correspond to 0.16 and 0.32 µM (or 160 and 320 nM) Δ^9-THC, respectively. Plasma concentrations of Δ^9-THC are known to vary widely across individuals, and diminish more rapidly by the smoking route than by oral administration. With respect to doses expressed in mg/kg of body weight, a daily oral dose of 2.5 mg of dronabinol (Δ^9-THC) can be estimated to correspond to a dose of approximately 0.04 mg/kg (assuming a body weight of 70 kg), whereas a daily oral dose of 40 mg of dronabinol would correspond to a dose of approximately 0.6 mg/kg of dronabinol. Smoking a 1 g joint containing 12.5% Δ^9-THC would correspond to a hypothetical dose of 1.8 mg/kg Δ^9-THC.

The following paragraphs summarize the main findings from a number of pre-clinical *in vitro* and *in vivo* studies of cannabinoids in neoplastic diseases. Clinical data are presented at the end of this section.

Pre-clinical data

In vitro studies suggest that Δ^9-THC decreases cell proliferation and increases cell death in human glioblastoma multiforme cell lines, with CB receptor activation accounting for only part of the observed effects (823). In the case of astrocytomas, higher concentrations were deemed to be clinically preferable because this would bypass CB receptor activation and induce apoptosis in all astrocytoma cell sub-populations (824). In the case of breast cancer, Δ^9-THC reduced human breast cancer cell proliferation at concentrations of 4 - 10 µM (i.e. 4 000 – 10 000 nM), with more aggressive estrogen receptor-negative tumour cells being more sensitive to the effects of THC (825). In contradistinction, another study showed that Δ^9-THC (50 µM (i.e. 50 000 nM) *in vitro* or 50 mg/kg *in vivo*) enhanced breast cancer growth and metastasis (826). Furthermore, Δ^9-THC, CBD, and CBN all stimulated breast cancer cell proliferation at concentrations ranging from 5 - 20 µM (i.e. 5 000 – 20 000 nM) (827), but this effect appeared to depend to some extent on the hormonal milieu (with lower estrogen levels promoting, and higher estrogen levels inhibiting growth). On the other hand, cannabinoids such as cannabigerol, cannabichromene, cannabidiolic acid, and THC acid as well as cannabinoid-based extracts enriched in either Δ^9-THC or CBD inhibited cell proliferation (in the micromolar range) in a number of different breast cancer cell lines (828). In *in vitro* studies examining the role of cannabinoids in lung cancer, Δ^9-THC (10 - 15 µM) (i.e. 10 000 – 15 000 nM) attenuated growth factor-induced migration and invasion of non-small cell lung cancer cell lines (829). In the case of colorectal cancer, Δ^9-THC at concentrations of 2.5 µM (i.e. 2 500 nM) and above (range: 7.5

- 12.5 μM) (i.e. 7 500 – 12 500 nM) were associated with a decrease in colorectal cancer cell survival, whereas lower concentrations (100 nM - 1 μM) had no effect (830). Taken together, these and other *in vitro* studies suggest cannabinoids can have complex biological effects in the context of malignancies. Differences in experimental conditions, cancer cell type, CB-receptor expression, hormonal levels, and the existence of CB-receptor dependent and independent regulatory mechanisms all appear to affect the control of growth, proliferation, and invasion of cancer cells in response to cannabinoids. Furthermore, these findings also suggest that the effective inhibitory concentrations of Δ^9-THC seen *in vitro* are between ~ 10 and 7 500 times higher than the concentrations of Δ^9-THC seen clinically, depending on the route of administration.

A pre-clinical *in vivo* study in rats showed that intra-tumoural administration of Δ^9-THC caused significant regression of intra-cranial malignant gliomas, and an accompanying increase in animal survival time without any neurotoxicity to healthy tissues (831). Furthermore, no substantial change was observed in certain behavioural measures suggesting that the effect of Δ^9-THC was limited to diseased neural tissues (831). Other studies showed that peritumoural administration of 0.5 mg Δ^9-THC /day, twice per week, for 90 days, significantly slowed focal breast tumour growth, blocked tumour generation, decreased total tumour burden, delayed the appearance of subsequent tumours, and impaired tumour vascularization in the ErbB2-positive metastatic breast cancer mouse model (832). Δ^9-THC, at doses of 5 mg/kg/day, administered intra-peritoneally or intra-tumourally also dramatically decreased the growth and metastasis as well as the vascularization of xenografted non-small cell lung cancer cell lines in immunodeficient mice (829). CBD (5 mg/kg) or CBD-rich extract (6.5 mg/kg) administered intra-tumourally or intra-peritoneally, twice per week, to breast-cancer-cell-xenografted athymic mice significantly decreased both tumour volume and the number of metastatic nodules (828). Other investigators showed that intra-peritoneal administration of CBD at 1 or 5 mg/kg/day significantly reduced the growth and metastasis of an aggressive breast cancer cell line in immune-competent mice (833). Importantly, the primary tumour acquired resistance to the inhibitory properties of CBD by day 25 of treatment (833). Taken together, these studies suggest that cannabinoids such as Δ^9-THC and CBD can, under a specific set of circumstances, have anti-neoplastic effects in various animal models of cancer at certain doses or concentration ranges.

Combining cannabinoids with other chemotherapeutic agents

Pre-clinical *in vitro* and *in vivo* studies investigating the effects of combining cannabinoids with frequently used chemotherapeutic agents have also been performed. One *in vitro* study showed that combining sub-maximal doses of Δ^9-THC (0.75 μM) with cisplatin or doxorubicin reduced the viability of an astrocytoma cell line in a synergistic manner (834). Likewise, combining sub-maximal doses of Δ^9-THC with temozolomide reduced the viability of several human glioma cell lines and primary cultures of glioma cells derived from human glioblastoma multiforme biopsies *in vitro* (835). Complementing these findings, an *in vivo* study showed that combined treatment with Δ^9-THC (15 mg/kg/day) and temozolomide (5 mg/kg/day) reduced the growth of glioma tumour xenografts in mice in a synergistic manner (835).

Clinical data

There is only one report of a clinical study of Δ^9-THC to treat cancer (836). In this non-placebo controlled 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 Δ^9-THC intra-tumourally per day (with doses of up to 80 - 180 μg Δ^9-THC per day). Median treatment duration was 15 days (836). While intra-tumoural administration of Δ^9-THC appeared to be well tolerated, the effect of Δ^9-THC on patient survival was not significantly different from that observed in other studies using chemotherapeutic agents such as temozolomide or carmustine (837,838). Nevertheless, *in vitro*, Δ^9-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 (836,839). In addition, results from a separate *in vitro* study suggest that CBD enhanced the inhibitory effects of Δ^9-THC on human glioblastoma cell proliferation and survival (839).

Despite the evidence presented in these and other studies, there is a general consensus that Δ^9-THC would not be considered the most appropriate CB agonist in anti-tumoural strategies, especially if administered systemically, because of its high hydrophobicity, relatively low agonist potency, and its well-known psychoactive properties (814,840,841). Much remains to be known regarding factors such as the expression levels of the cannabinoid receptors in different cancers, the effects of different cannabinoids on different cancer cell types, the identification of factors that confer resistance to cannabinoid treatment, as well as the most efficient approaches for enhancing cannabinoid anti-tumoural activity whether alone or in combination with other therapies (828,840). Furthermore, the apparent biphasic effect of cannabinoids further highlights the need for more comprehensive dose-response studies (842).

4.8.10 Emerging Potential Therapeutic Uses

There are a few pre-clinical reports which suggest that administration of a low dose of THC, a CB_1 receptor antagonist, or a CB_2 receptor agonist may reduce the progression of atherosclerosis in mouse models of the disease (843,844,845). Oral administration of THC (1 mg/kg/day) has been associated with significant inhibition of disease progression in the apolipoprotein E (ApoE) knockout mouse, a mouse model of atherosclerosis (843). The beneficial effect of THC in this study was mediated by the CB_2 receptor, likely through its inhibitory effects on immune system cells (macrophages and T-cells) located in or near atherosclerotic lesions (843). These findings were supported by another study which showed that intra-peritoneal administration of a synthetic CB_1/CB_2 receptor agonist significantly reduced aortic plaque area in the ApoE knockout mouse (845). Administration of the CB receptor agonist reduced macrophage infiltration into the atherosclerotic plaque, and reduced the expression of vascular cellular adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), and P-selectin in the aorta, as well as reducing macrophage adhesion (845). Again, the observed beneficial effects appeared to be mediated by activation of the CB_2 receptor (845). A separate study confirmed the atheroprotective effects of selective CB_2 receptor activation by demonstrating increased vascular leukocyte infiltration in atherosclerotic plaques in mice lacking both the ApoE and CB_2 receptors compared to ApoE knockout mice, and decreased atherosclerotic plaque formation and reduced vascular superoxide release in ApoE knockout mice treated with a CB_2 receptor selective agonist (846). In contrast to these findings, a different study showed that activation or deletion of the CB_2 receptor did not modulate atherogenesis in the LDL receptor knockout mouse model of atherosclerosis (847). Another study suggested that the CB_2 receptor, while not affecting the size of atherosclerotic lesions in LDL receptor knockout mice, did increase lesional macrophage accumulation and smooth muscle cell infiltration, as well as reduce lesional apoptosis and alter the extra-cellular matrix of lesions (848). The findings from this study suggested that while the CB_2 receptor did not play a significant role in the initial formation of atherosclerotic lesions, it did play a role in modulating the progression of the disease (848). On the other hand, activation of the CB_1 receptor is associated with the release of reactive oxygen species and endothelial cell death (849), and CB_1 receptor blockade by rimonabant in ApoE knockout mice was associated with a significant reduction in the relative size of aortic atherosclerotic lesions (844). In conclusion, it appears that in the case of atherosclerosis, the CB_1 and CB_2 receptors play opposing roles—the CB_1 receptor appears to be atherogenic, whereas the CB_2 receptor appears to be anti-atherogenic (844,846,849,850,851) although some controversy still remains regarding the exact role played by the CB_2 receptor (852). Cannabidiol has also been shown to potently inhibit the activity of the enzyme 15-lipoxygenase, which has been implicated in the pathophysiology of atherogenesis (850,853). Further studies are needed in this area.

5.0 Precautions

The contraindications that apply to those considering using prescription cannabinoid-based therapies (such as nabilone (Cesamet®), nabiximols (Sativex®) or dronabinol (Marinol®)) also apply to those considering using cannabis. Currently, no clinical guidelines exist with respect to monitoring patients who are taking cannabis for therapeutic purposes.

The risk/benefit ratio of using cannabis 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:

- Cannabis should not be used in any person under the age of 18, or in any patient who has a history of hypersensitivity to any cannabinoid or to smoke. The adverse effects of cannabis use on mental health are greater during development, particularly during adolescence, than in adulthood (146,686,690) (see also section 7.7.3).
- Cannabis should not be used in patients with severe cardio-pulmonary disease because of occasional hypotension, possible hypertension, syncope, or tachycardia (117,233,234).
- Smoked cannabis is not recommended in patients with respiratory insufficiency such as asthma or chronic obstructive pulmonary disease (243).
- Cannabis should not be used in patients with severe liver or renal disease. 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 (32,854).
- Cannabis should not be used in patients with a personal history of psychiatric disorders (especially schizophrenia), or a familial history of schizophrenia.
- Cannabis should be used with caution in patients with a history of substance abuse, including alcohol abuse, because such individuals may be more prone to abuse cannabis, which itself, is a frequently abused substance (675,855,856).
- Patients with mania or depression and using cannabis or a cannabinoid should be under careful psychiatric monitoring (139,143,857).
- Cannabis should be used with caution in patients receiving concomitant therapy with sedative-hypnotics or other psychoactive drugs because of the potential for additive or synergistic CNS depressant or psychoactive effects (169,170,171) (also see section 7.7). Cannabis may also exacerbate the CNS depressant effects of alcohol and increase the incidence of adverse effects (see section 7.7). Patients should be advised of the negative effects of cannabis/cannabinoids on memory and to report any mental or behavioural changes that occur after using cannabis (178,181).
- Cannabis is not recommended 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 (see sections 6.0 and 7.4).

6.0 Warnings

Cannabis is one of the most widely abused illicit drugs, and can produce physical and psychological dependence (122,156,210,858,859). The drug has complex effects in the CNS and can cause cognitive and memory impairment, changes in mood, altered perception, and decreased impulse control (152,180,860,861). Patients should be supervised when administration is initiated.

Dosing: In the case of smoked/vapourized cannabis, the dose required to achieve therapeutic effects and avoid adverse effects is difficult to estimate and is affected by the source of the plant material, its processing, and by different smoking techniques. These techniques include depth of inhalation, duration of breath-holding and the number and frequency of puffs, as well as how much of the cigarette is smoked or how much plant material is vapourized. Smoking or vapourization should proceed slowly and cautiously in a gradual fashion and should cease if the patient begins to experience the following effects: disorientation, dizziness, ataxia, agitation, anxiety, tachycardia and orthostatic hypotension, depression, hallucinations, or psychosis. There is also insufficient information regarding oral dosing, but the patient should be made aware that the effects following oral administration only begin to be felt 30 min to 1 h or more after ingestion, and that consumption of cannabis-based products (e.g. cookies, baked goods) should proceed slowly, and that edibles should be consumed only in small amounts at a time in order to gauge the effects and to prevent overdosing.

Psychosis: Anyone experiencing an acute psychotic reaction to cannabis or cannabinoids should promptly stop taking the drug and seek immediate medical attention. A psychotic reaction is defined as a loss of contact with reality characterized by one or more of the following: changes in thinking patterns (difficulty concentrating, memory loss, and/or disconnected thoughts), delusions (fixed false beliefs not anchored in reality), hallucinations (seeing, hearing, tasting, smelling or feeling something that does not exist in reality), changes in mood (intense bursts of emotion, absence of, or blunted emotions), very disorganized behaviour or speech, and thoughts of death and suicide (341).

Occupational hazards: Patients using cannabis should be warned not to drive or to perform hazardous tasks, such as operating heavy machinery, because impairment of mental alertness and physical coordination resulting from the use of cannabis or cannabinoids may decrease their ability to perform such tasks (182). Depending on the dose, impairment can last for over 24 h after last use because of the long half-life of Δ^9-THC (62,131,290,862,863). Furthermore, impairment may be exacerbated with co-consumption of other CNS depressants (e.g. benzodiazepines, barbiturates, opioids, anti-histamines, muscle relaxants, or ethanol) (114,170,174,864,865,866).

Pregnancy: Pre-clinical studies suggest that endocannabinoid tone plays a critical role in fertilization, oviductal transport, implantation, and fetal/placental development (reviewed in (867)). One pilot clinical study suggested that high circulating levels of anandamide were associated with an increased incidence of miscarriage (868). Thus, there is a risk that maternal exposure to cannabis or cannabinoids could potentially adversely affect conception and/or maintenance of pregnancy. In addition, the use of cannabis during pregnancy should be avoided as there is some evidence of long-term developmental problems in children exposed to cannabis *in utero* (869,870). Men, especially those on the borderline of infertility and intending to start a family, are cautioned against using cannabis since exposure to cannabis or THC could potentially reduce the success rates of intended pregnancies (see section 7.4).

Lactation: Cannabinoids are excreted in human milk and may be absorbed by the nursing baby (871,872). Because of potential risks to the child, nursing mothers should not use cannabis.

6.1 Tolerance, dependence, and withdrawal symptoms

Tolerance, psychological, and physical dependence can occur with prolonged use of cannabis (118,210). Tolerance to cardiovascular effects occurs quickly, but dependence is slower to develop and appears more likely with higher, more frequent dosing (219,220). See section 2.4 for further information on tolerance, dependence, and withdrawal symptoms.

6.2 Drug interactions

The most clinically significant interactions may occur when cannabis is taken with other CNS depressant drugs such as sedative-hypnotics or alcohol (114,169,170,171,864,865,866,873,874). An overdose can occur if a patient is smoking/vapourizing cannabis and consuming orally administered cannabinoids, whether from prescription cannabinoid medications (e.g. dronabinol, nabilone), or from consumption of teas, baked goods or other products (174,290).

Xenobiotic-mediated inhibition or potentiation of cannabinoid metabolism

Δ^9-THC is oxidized by the xenobiotic-metabolizing cytochrome P450 (CYP) mixed-function oxidases 2C9, 2C19, and 3A4 (62). Therefore substances that inhibit these CYP isoenzymes such as certain anti-depressants (e.g. fluoxetine, fluvoxamine, and nefazodone), proton pump inhibitors (e.g. cimetidine and omeprazole), macrolides (e.g. clarithromycin and erythromycin), anti-mycotics (e.g. itraconazole, fluconazole, ketoconazole, miconazole), calcium antagonists (e.g. diltiazem, verapamil), HIV protease inhibitors (e.g. ritonavir), amiodarone, and isoniazid can potentially increase the bioavailability of Δ^9-THC as well as the chance of experiencing THC-related side effects (289,875,876). On the other hand, drugs that accelerate Δ^9-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 (289,876).

Cannabinoid–mediated regulation of drug metabolism and drug transport

THC, CBD, and CBN are known to inhibit CYP isozymes such as CYP1A1, 1A2, and 1B1 (58). Cannabis may therefore increase the bioavailability of drugs metabolized by these enzymes. Such drugs include amitryptiline, phenacetin, theophylline, granisetron, dacarbazine, and flutamide (58). THC, carboxy- Δ^9-THC, CBD, and CBN all stimulate, and in some cases even inhibit, the activity of the drug transporter P-glycoprotein *in vitro* (56). This suggests a potential additional role for these cannabinoids in affecting the therapeutic drug efficacy and toxicity of co-

administered drugs (56). Clinicians should therefore be aware other medications that the patient is taking and carefully monitor patients using other drugs along with cannabis or cannabinoids.

Cannabinoid-opioid interaction

Patients taking fentanyl (or related opioids) and anti-psychotic medications (clozapine or olanzapine) may also be at risk of experiencing adverse effects if co-consuming cannabis/cannabinoids (322,323,324,503,877). In one study, subjects reported an increase in the intensity and duration of the "high" when oxycodone was combined with inhalation of vapourized cannabis; this effect was not observed when morphine was combined with inhalation of vapourized cannabis (187). In that study, inhalation of vapourized cannabis was associated with a statistically significant decrease in the maximum concentration (C_{max}) of sustained-release morphine sulfate, and the time to C_{max} for morphine was also delayed, although the delay was not statistically significant (187). There were no changes in the AUC for morphine metabolites, or in the ratio of morphine metabolites to parent morphine (187). In contrast to the effects seen with morphine sulfate, inhalation of vapourized cannabis was not associated with any changes in oxycodone pharmacokinetics (187).

Evidence from pharmacogenetic studies

Pharmacogenetic studies have suggested that patients homozygous for the *CYP2C9*3* allele appear to have impaired THC metabolism and may show greater intoxication than **1/*3* heterozygotes or **1/*1* homozygotes (318).

Data from clinical studies

A significant proportion of published clinical studies of cannabis or prescription cannabinoid medications have used patient populations that were taking concomitant medications for a variety of disorders such as neuropathic pain of various etiologies (142,168,172,186,187,261,292,364,494,501,502,503), cancer-related pain (112,349,509), fibromyalgia (158,261,353,354), pain and spasticity associated with multiple sclerosis (188,262,291,361,428,504), and symptoms associated with Huntington's or Parkinson's disease (586,595). Examples of commonly-used medications seen in clinical trials of cannabis or prescription cannabinoid medications (e.g. dronabinol, nabilone and nabiximols) include non-steroidal anti-inflammatory drugs (e.g. acetaminophen, COX-2 inhibitors), metamizol, topical steroids, muscle relaxants, short- and long-acting opioids (e.g. codeine, morphine, hydromorphone, oxycodone, oxycontin, tramadol, fentanyl, methadone), ketamine, anti-convulsants (e.g. gabapentin, pregabalin), anti-depressants (e.g. tricyclics, selective-serotonin re-uptake inhibitors, serotonin-norepinephrine re-uptake inhibitors, serotonin-antagonist re-uptake inhibitors), and anxiolytics. According to the cited clinical studies, concomitant use of cannabis or prescription cannabinoid medications with other medications was reported to be well tolerated, and many of the observed adverse effects were those typically associated with the psychotropic effects of cannabis and cannabinoids (e.g. transient impairment of sensory and perceptual functions, abnormal thinking, disturbance in attention, dizziness, confusion, sedation, fatigue, euphoria, dysphoria, depression, paranoia, hallucinations, dry mouth, anxiety, hypotension, tachycardia, headache, throat irritation).

6.3 Drug screening tests

Because of the long half-life of elimination of cannabinoids and their metabolites, drug tests screening for cannabinoids can be positive for weeks after last cannabis/cannabinoid use (878,879) depending on the sensitivities of the tests used.

7.0 Adverse Effects

There is generally far more information available in the medical literature on the adverse effects associated with recreational cannabis use than there is with therapeutic cannabis use. Accordingly, much of the information presented below regarding the adverse effects of cannabis use comes from studies carried out among recreational users. Much less information on the adverse effects associated with the use of cannabis for therapeutic purposes comes from clinical studies, mainly because of the small number of such studies that have been carried out to date. Furthermore, while there is some information on the short-term adverse effects associated with the use of cannabis for therapeutic purposes, much less information exists on the long-term consequences of cannabis use for therapeutic purposes because all of the available clinical studies were short-term. A Canadian systematic review of the adverse effects of prescription cannabinoid medications concluded that the rate of non-serious adverse events was almost two-fold higher among those patients using prescription cannabinoid medications compared to controls (880). The most frequently cited adverse events associated with the use of prescription cannabinoid medications were nervous system disorders, psychiatric disorders, gastrointestinal disorders, and vascular and cardiac disorders (880). An additional consideration in the evaluation of adverse effects associated with cannabis use is the concomitant use of tobacco and alcohol as well as other drugs, whether they are non-prescription, prescription, or illicit drugs (122,881,882,883,884) (and also see section 6.2).

7.1 Carcinogenesis and mutagenesis

Qualitatively, cannabis smoke condensates have been shown to contain many of the same chemicals as tobacco smoke (70). Furthermore, a number of *in vitro* studies have provided strong evidence that smoke from burning cannabis is carcinogenic (reviewed in (118)). More recently, the cytotoxic and mutagenic potential of cannabis smoke condensates were compared to their tobacco counterparts (68). In contrast to tobacco smoke condensates, those derived from cannabis smoke appeared to be more cytotoxic and mutagenic, while the opposite was true with respect to cytogenetic damage (68). In addition, for either cannabis or tobacco smoke, the particulate phase was substantially more cytotoxic than the gas phase. Together, these studies suggest that cannabis smoke cannot be deemed "safer" than tobacco smoke.

Despite some persuasive *in vitro* data, the epidemiological evidence for a link between cannabis smoking and cancer remains inconclusive because of conflicting results from a limited number of studies. One epidemiological study in relatively young clients of a health maintenance organization (HMO) found an increased incidence of prostate cancer in those men who smoked cannabis and other non-tobacco materials (238). No other associations were found between cannabis use and other cancers; however, the study was limited by the demographics of the HMO clientele and the very low cannabis exposure threshold employed in the study to define "users". A case-control study suggested that cannabis smoking may increase the risk of head and neck cancer (Odds Ratio = 2.6; Confidence Interval = 1.1 - 6.6), with a strong dose-response pattern compared to non-smoking controls (239). However, the authors note a number of limitations with their study such as underreporting, inaccurate cannabis dose reporting, assay sensitivity, and low power. A large population-based case-control study, carried out in the year 2006, of 1 212 incident cancer cases and 1 040 cancer-free matched controls did not find a significant relationship between long-term cannabis smoking and cancers of the lung and upper aerodigestive tract (240). However, a smaller case-control study carried out in 2008 in young adults (≤ 55 years of age), examined 79 cases of lung cancer and 324 controls and reported that the risk of lung cancer increased by 8% (95% Confidence Interval = 2 - 15%) for each "joint-year" (defined as the smoking of one joint per day for one year) after adjusting for cigarette smoking (241). Despite the conflicting evidence surrounding the carcinogenic potential of cannabis smoke in humans, it is advisable to limit the degree to which cannabis is smoked. Further well-controlled epidemiological studies are required to better establish whether there is causality between cannabis smoking and carcinogenesis in human populations. Lastly, in the case of cancer patients, the potential risks of carcinogenesis and mutagenesis associated with smoking cannabis must be weighed against any potential therapeutic benefits for this patient population; routes of administration other than smoking (e.g. vapourization, oral administration) may warrant consideration. Because vapourization is a lower-temperature process compared with pyrolysis (i.e. smoking), vapourization appears to be associated with 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 Δ^9-THC from the cannabis material (273,281,282,283,284).

7.2 Respiratory tract

Differences in the smoking techniques used by cannabis vs. 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 (885). A systematic comparison of the mainstream smoke composition from cannabis (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 (70). The "standard" condition reflects typical tobacco cigarette smoking conditions, whereas the "extreme" condition approaches that typically seen in cannabis smoking (70). Ammonia in mainstream cannabis smoke was 20-fold greater than that found in tobacco smoke, and oxides of nitrogen and hydrogen cyanide were three to five times higher in cannabis smoke vs. tobacco smoke. Carbon monoxide was significantly lower in mainstream cannabis smoke, under both smoking conditions. Tar was statistically significantly higher in mainstream cannabis smoke but only under the "extreme" smoking condition.

Mucosal biopsy specimens taken from chronic cannabis smokers, who reported smoking only cannabis, showed a number of histopathologic changes including basal cell hyperplasia, stratification, goblet cell hyperplasia, cell disorganization, inflammation, basement membrane thickening, and squamous cell metaplasia (242). 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 the forced expiratory volume in 1 second (FEV_1), an increase in airway resistance, and a decrease in airway conductance (244,245,246). 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 (122,886). All changes were most evident in heavy chronic users, defined as those who smoked more than three joints per day for 25 years (238,887), although evidence of measurable respiratory symptoms (e.g. decreased FEV_1/FVC ratio) was also observed in young, cannabis-dependent individuals whose smoking behaviour was comparable to tobacco smokers consuming 1 - 10 cigarettes/day (888). The potential risk of developing chronic obstructive respiratory disease, with long-term use and/or dependence, has been claimed to be potentially as great as among tobacco users (888). However, a recently published longitudinal study collecting repeated measurements of pulmonary function and smoking over a period of 20 years, in a cohort of 5 115 men and women in four U.S. cities (the CARDIA study), suggested a more complex picture. The study found a non-linear association between marihuana smoking and pulmonary function (247). By comparison, tobacco smoking (current and lifetime) was linearly associated with lower FEV_1 and FVC (247). Low levels of cumulative marihuana smoking were not associated with adverse effects on pulmonary function. Instead, at this level, marihuana smoking was associated with an increase in the FEV_1 and FVC values (247). At up to seven "joint-years" (a "joint-year" defined as smoking one joint/day, 365 days/year) of *lifetime* exposure there was no evidence of decreased pulmonary function. However, heavy chronic marihuana smoking (> ~30 joint-years or > ~25 smoking episodes per month) was associated with an accelerated decline in pulmonary function (FEV_1 but not FVC) (247).

Further research is needed to clarify the complex changes in lung function found in cannabis smokers, and to determine if there is a cause and effect relationship between cannabis smoking and the development of lung disease. Smoking cannabis may also increase the risk of developing respiratory infections in chronic users (889) through exposure to infectious organisms such as fungi and molds which can be found in the plant material (890), or alternatively by decreasing natural host defenses (891). However, further epidemiological research is also required to establish a causal relationship between cannabis smoking and respiratory infections. Vapourization of cannabis may be considered an alternative to smoking, although research is required to determine if there are any adverse effects of vapourization on lung health/function. For additional information on vapourization please consult sections 1.1.1, 1.1.2, 2.2.1.2, 3.4, 4.6.2.3, and **Table 6**.

7.3 Immune system

Pre-clinical studies

Evidence from *in vivo* and *in vitro* studies suggests complex and apparently dichotomous roles for the endocannabinoid system on immune system function (24). First, CB_1 and CB_2 receptors are known to be expressed in various immunocytes (B cells, monocytes, neutrophils, T lymphocytes, macrophages, mast cells), with CB_2 receptor expression generally being more abundant than CB_1 receptor expression; the ratio of CB_2 to CB_1 receptor expression ranges between 10 - 100 : 1 respectively, depending on the immune cell type in question (24,25). Second, immune cells also have the ability to synthesize, secrete, transport and catabolize endocannabinoids (24). Third, while stimulation of the CB_2 receptor appears to be generally associated with immunosuppressive effects, activation of the CB_1 receptor appears to be associated with an opposing immunostimulatory effect (24). Fourth, whereas certain cannabinoids have been shown to modulate the release of pro- or anti-inflammatory cytokines, pro-inflammatory cytokines (such as TNF-α) have, in turn, been reported to affect the functioning of the endocannabinoid system by upregulating the expression of both CB_1 and CB_2 receptor mRNA and protein levels (25). Thus, there appears to be some level of cross-talk between

the endocannabinoid and immune systems. Fifth, as is the case in other situations, Δ^9-THC appears to have a biphasic effect on immune system function. Low doses of Δ^9-THC seem to have stimulatory or pro-inflammatory effects, while higher doses appear to have inhibitory or immunosuppressive effects (266). Both Δ^9-THC and CBD have been reported to modulate cell-mediated and humoural immunity, through CB receptor-dependent and CB receptor-independent mechanisms (266,892,893). Cannabinoids target various cellular signaling and transcriptional pathways resulting in the inhibition of pro-inflammatory cytokine release (e.g. IL-1β, IL-6, IFN-β), and/or stimulation of anti-inflammatory cytokine release (e.g. IL-4, IL-5, Il-10, IL-13) (25,266). CBD also appears to induce a shift in Th1/Th2 immunobalance (892). While under certain circumstances, cannabinoids may appear to have broad anti-inflammatory and immunosuppressive functions which could be of benefit in pathological conditions having inflammatory characteristics, such beneficial functions may become problematic in the context of essential defensive responses to infections (24). For example, *in vitro* as well as *in vivo* experiments suggest cannabinoids have an impact on virus-host cell interactions (894): cannabinoid treatment was associated with increased viral replication of HSV-2, HIV-1, KSHV, influenza, and VSV viruses, or was associated with increases in surrogate measures of infection in these experimental models (895,896,897,898,899,900).

Taken together, the available information suggests that differences in the observed effects of cannabinoids on immune system function (i.e. immunosuppressive vs. immunostimulatory) may be explained by differences in the routes/methods of administration (smoked, oral, or other route), the length of exposure to the cannabinoid(s), the dose and type of cannabinoid used and which receptors are preferentially targeted, but also by differences between species, the experimental protocols and outcome measures that were used, and for clinical studies the health status/medical condition of the human subjects (266).

Clinical studies

The effects of cannabis smoking on the human immune system have been studied, but to a very limited degree. A major concern with HIV-positive cannabis smokers, or patients undergoing cancer chemotherapy, is that they might be more vulnerable than other cannabis smokers to the immunosuppressive effects of cannabis or that they risk exposure to infectious organisms associated with cannabis plant material (378). A group of studies has partially addressed the former concern. In one study, HIV-positive patients on stable anti-retroviral therapy were randomized to smoked cannabis or oral dronabinol and 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 (901). A longitudinal study of 481 HIV-infected men who used cannabis and who were followed over an average five-year period found that while cannabis use was generally associated with a higher CD4+ cell count in infected men and controls, no clinically meaningful associations, adverse or otherwise, between cannabis use and T-cell counts and percentages could be established (902). Cannabis use was also not associated with an increased rate of progression to AIDS in HIV-infected individuals (903). In another study, smoking cannabis was associated with lower plasma concentrations of the protease inhibitors indinavir and nelfinavir; dronabinol or placebo had no effect (322). However, the decreased protease inhibitor levels were not associated with an elevated viral load, or changes in CD4+ or CD8+ cell counts (390).

In humans, smoking cannabis was also associated with poorer outcome in patients with chronic hepatitis C (882,904). Although pre-clinical studies strongly suggest that cannabinoids have broad immunomodulatory effects, and raise the possibility that cannabinoids may affect the ability of immunosuppressed patients to successfully resist or combat infections, it is unclear at this time if the immunomodulatory effects seen both pre-clinically and clinically translate into any clinically significant adverse outcomes.

Clear predictions concerning the effects of cannabinoids in those individuals who suffer from a dysregulated immune system are difficult to make because of the relative lack of available, comprehensive information on the subject. The clinician must therefore weigh the potential benefits of using cannabis and/or cannabinoids against the possible risks of using these substances on a case-by-case basis.

A recent cross-sectional study examined the association between cannabis use status and adherence to anti-retroviral therapy as well as the association between cannabis use status, HIV symptoms, and side effects associated with anti-retroviral therapy among a sample of HIV-positive individuals (905). The study reported that those subjects who had a cannabis use disorder (according to DSM-IV criteria and a Marijuana Smoking History Questionnaire score indicating daily cannabis or use more than once per day) had a significantly lower adherence to treatment than those who reported using cannabis once per week or more, but less than daily or not at all (905). Those who had a cannabis use disorder also had a higher viral load than those who used cannabis less than daily but at least once per week, as well as those who did not use at all; absolute CD4 count was not significantly different between groups (905). Furthermore, those

subjects with a cannabis use disorder reported significantly more frequent and severe HIV symptoms and/or medication side effects than those who used cannabis less than daily (but at least once per week), or those who reported not using cannabis at all (905). One limitation to this study was its cross-sectional nature, precluding the ability to establish a cause-and-effect relationship.

7.4 Reproductive and endocrine systems

Role of the endocannabinoid system in sexual physiology

The CB_1 receptor is widely expressed in various brain structures such as the striatum, hippocampus, and the cerebellum, as well as the amygdala, the midbrain, and the cerebral cortex—all structures that play various roles in regulating different aspects of sexual behaviour and function (269). For example, CB_1 receptors within the striatum and cerebellum may regulate motor activity and function; CB_1 receptors located within corticolimbic structures (e.g. pre-frontal cortex, amygdala and hippocampus) may regulate stress responsivity and emotional behaviour; CB_1 receptors located within the dorsal raphe and ventral tegmental area may regulate genital reflexes, sexual motivation and inhibition; and lastly, CB_1 receptors expressed within the hypothalamus and the pituitary gland may modulate the functioning of the hypothalamic-pituitary-gonadal axis either directly through modulation of gonadotropin-releasing hormone or indirectly through other modulators (269,270).

CB_1 receptor-mediated modulation of the hypothalamic-pituitary axis results in the suppression of luteinizing hormone, thyroid stimulating hormone, growth hormone, and prolactin release from the pituitary gland, while the effects on follicle stimulating hormone are seemingly unclear but point to a probable suppression of release (268,906). In animals, these effects are accompanied by changes in reproductive function and behaviour including decreases in plasma testosterone levels, degenerative changes in spermatocytes and spermatids, anovulation, and potential reduction in copulatory behaviour (268,270). Aside from the roles of the cannabinoid receptors in the brain, the male and female reproductive systems also contain an endocannabinoid system, and increasing experimental evidence suggests important roles for the endocannabinoid system in regulating various reproductive functions such as folliculogenesis, spermatogenesis, ovulation, fertilization, oviductal transport, implantation, embryo development, pregnancy, and labour (reviewed in (37)).

Effects of cannabis on human sexual behaviour

There is a relative paucity of data with regards to the effects of cannabis or cannabinoids on human sexual behaviour. One review article has summarized the few available studies on the subject (269). It concluded that in general, the effects of cannabis on sexual functioning and behaviour appear to be dose-dependent. For women, the available information suggests beneficial effects on sexual behaviour and functioning (e.g. reported increases in sensitivity to touch and relaxation and a corresponding increase in sexual responsiveness) at low to moderate doses, and potentially opposite responses at higher doses (269). For men, the available information suggests that cannabis intake at low to moderate doses may facilitate sexual desire and activity, but that at higher doses or with more frequent or chronic use it may inhibit sexual motivation as well as erectile function (269). Results obtained from animal studies appear to mirror some of these findings, although exceptions have also been noted (269). Although the effects of cannabis on human sexual behaviour are still not well understood, some of its reported beneficial effects have been speculatively linked to its psychoactive properties (e.g. increase in tactile sensitivity/perception or slowing of temporal perception) or alternatively, to a loss of inhibitions and an increased state of relaxation (269).

Studies investigating the effects of cannabis consumption on testosterone levels in men have yielded conflicting results (269). While some investigators have found that acute or chronic cannabis consumption significantly lowered plasma testosterone levels in a dose-dependent manner, others have apparently failed to find similar effects (269). Differences in the reported effects of cannabis on testosterone levels among the various studies have been, in part, attributed to differences in the experimental protocols employed (269).

Effects on sperm and testicular health

The effects of cannabis and Δ^9-THC on human sperm have been investigated both *in vivo* and *in vitro* (907,908,909). A significant decline in sperm count, concentration and motility, and an increase in abnormal sperm morphology were observed in men who smoked cannabis (8 - 20 cigarettes/day) for four weeks (907). 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 sub-population (909). Decreased sperm motility was observed in both fractions at Δ^9-THC concentrations mimicking those attained recreationally (0.32 and 4.8 μM), and in the 45% fraction at Δ^9-THC concentrations typically seen therapeutically (0.032 μM). Inhibition of the acrosome

reaction was only observed at the highest Δ^9-THC concentration tested (4.8 μM) in the 90% fraction, while the 45% fraction displayed decreased acrosome reactions at all three Δ^9-THC concentrations tested. Such effects carry the possibility of impairing crucial sperm functions and male fertility, especially in those males already on the borderline of infertility (909).

A recently published, population-based, case-control study reported that compared with men who never used cannabis, those who had reported ever-using had a nearly two-fold increased risk of developing testicular germ-cell tumours of any histologic type (Odds Ratio = 1.94, 95% Confidence Interval: 1.02 - 3.68) and a greater than two-fold increased risk of non-seminoma or mixed germ-cell tumours (Odds Ratio = 2.42, 95% Confidence Interval: 1.08 - 5.42) (910). Men who reported using cannabis less than once per week appeared to have an elevated risk of developing testicular germ-cell tumours compared to those men who reported using cannabis more frequently. Men who reported using cannabis for a period under 10 years were also more than twice as likely to develop such tumours as those reporting ≥ 10 years of use (910).

Effects on foetal development and child development

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 (911,912,913,914) or a slightly increased risk of sudden infant death (915), while others report no effect (916,917,918). On the other hand, there appear to be some long-term effects on the development of children born to mothers who used cannabis during pregnancy. Two longitudinal investigations carried out over a time span of 20 years (reviewed in (869)) 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 findings were confirmed by a third study (870). These behavioural effects also appeared to have an adverse influence on aspects of executive function in later years.

Evidence suggests that cannabinoids accumulate in the breast milk of mothers who smoke cannabis and are transferred to newborns through breastfeeding (871,919). In a case-control study (920), exposure to cannabis from the mother's milk during the first month post-partum appeared to be associated with a decrease in infant motor development at one year of age.

7.5 Cardiovascular system

The most consistent acute physiological effect of smoking cannabis is dose-related tachycardia (121,226,232). While this is not usually considered dangerous for healthy young users, it may be dangerous to those already suffering from cardiac disorders or angina (118,921). Inhalation of cannabis smoke reduces the amount of exercise required to cause an angina attack by 50% (922), and has been associated with a five-fold increased risk of myocardial infarction in the first hour following smoking (232). This may be caused by a Δ^9-THC-related increase in cardiac output, myocardial oxygen demand, catecholamine levels, and carboxyhemoglobin as well as postural hypotension (226,227,923). 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 Δ^9-THC per day (equivalent to 80 - 100 mg of cannabis containing 10% Δ^9-THC), bradycardia (924) with a decrease in supine blood pressure was observed (925).

Cannabis is also known to cause peripheral vasodilatation, postural hypotension, and characteristic conjunctival reddening after smoking (926).

AIDS patients may be at an increased risk of experiencing adverse cardiovascular outcomes caused by interactions between cannabis and anti-retroviral drugs, such as ritonavir, which has been associated with adverse cardiovascular events (927).

There have been a number of case-reports of arteritis associated with long-standing, chronic, daily cannabis smoking (928,929,930,931). Case-reports have also suggested an association between chronic, daily cannabis smoking and multi-focal intracranial stenosis (932) and stroke (236,237).

7.6 Gastrointestinal system and Liver

7.6.1 Hyperemesis

There are an increasing number of case-reports being published regarding the "cannabis hyperemesis syndrome" (CHS). CHS is a condition observed in people chronically using cannabis on a daily basis, often for years, and is characterized by severe, intractable episodes of nausea and cyclic vomiting accompanied by abdominal pain (typically epigastric or periumbilical); these symptoms are relieved by compulsive hot water bathing or showering (194,195,196,197,198,199,200,201,202,203,204). The pathophysiology of CHS is not well understood (202). Treatment of patients presenting with this syndrome has been reported to include: recommending cessation of cannabis use, rehydration, and psychological counselling (200,202). The efficacy of anti-emetics such as metoclopramide, ondansetron, prochlorperazine, and promethazine in relieving the symptoms of nausea and vomiting in patients with CHS appears to be debatable (198,200,201,204). A recent case-report suggests that lorazepam (1 mg i.v., followed by 1 mg tablets b.i.d.) may provide some benefit in alleviating the symptoms of CHS, at least in the short-term (933).

7.6.2 Liver

A number of studies have strongly implicated the endocannabinoid system in chronic liver disease (934,935,936,937,938). Studies in patients with chronic hepatitis C have found a significant association between daily cannabis smoking and moderate to severe fibrosis (904), as well as cannabis smoking being a predictor of fibrosis progression (882). Another study showed that daily cannabis use was a predictor of steatosis severity in these individuals (854). Steatosis is an independent predictor of fibrosis progression and an established factor of poor response to anti-viral therapy (939). The authors recommend that patients with ongoing chronic hepatitis C be strongly advised to abstain from daily cannabis use.

In contrast, another study showed that modest cannabis use (defined as anything less than daily use in this study) was associated with an increase in the duration of time that patients remained on anti-retroviral treatment (252). This effect was postulated to contribute, at least in part, to an increase in the percentage of patients demonstrating a sustained virological response (i.e. the absence of detectable levels of hepatitis C virus RNA six months after completion of therapy) (252).

7.7 Central nervous system

The most frequently reported adverse events encountered with cannabinoids involve the central nervous system (CNS). Commonly reported CNS events in controlled clinical trials with dronabinol (Marinol®) and nabiximols (Sativex®) are intoxication-like reactions including drowsiness, dizziness, and transient impairment of sensory and perceptual functions (174,290). A "high" (easy laughing, elation, heightened awareness), which could be unwanted or unpleasant for patients, was reported in 24% of the patients receiving Marinol® as an anti-emetic, and in 8% of patients receiving it as an appetite stimulant (174). Other adverse events occurring at a rate of > 1% for Marinol® include anxiety/nervousness, confusion, and depersonalization (174). Dizziness, euphoria, paranoia, somnolence, abnormal thinking ranged from 3 - 10% (174). The rates of amnesia, ataxia, and hallucinations were > 10% when used as an anti-emetic at higher doses (174). 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% (940). All other intoxication-like effects are reported by less than 5% of users (with the exception of somnolence, 7%) (940). Other events reported for Sativex® include disorientation and dissociation. **Many, if not all, of the above-noted CNS effects also occur with cannabis.**

7.7.1 Cognition

The acute effects of cannabis use on cognition have been reviewed by Lundqvist (235). Cannabis impairs cognition involving faculties such as short-term memory, attention, concentration, executive functioning and visuoperception (180,941,942). 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 (943). Cannabis intoxication significantly impairs the ability to learn and recall word lists or short stories (944).

The long-term effects of cannabis on cognition remain controversial. Some studies report a positive association between cannabis consumption and cognitive deficits (945,946,947), or suggest that cognitive deficits persist after abstinence (180,941,948,949). Other studies did not find an association between cannabis use and long-term cognitive decline (948,949). 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 (950,951). Nonetheless, studies generally suggest that chronic cannabis users suffer varying degrees of cognitive impairment that have the potential to be long-lasting (127). Prolonged use of ingested or inhaled cannabis in patients with multiple sclerosis was associated with poorer performance on various cognitive domains (e.g. information processing speed, working memory, executive function, and visuospatial perception), according to a cross-sectional study (178). A recently published, prospective, longitudinal study investigating the association between persistent cannabis use and neuropsychological functioning in a birth cohort of 1 037 individuals followed over a period of 20 years found that persistent cannabis use beginning in adolescence was associated with statistically significant global neuropsychological decline across a number of domains of functioning (952). Furthermore, cessation of cannabis use, for a period of one year or more, did not appear to fully restore neuropsychological functioning among adolescent-onset persistent cannabis users (952).

7.7.2 Psychomotor performance

Although no studies have been carried out to date examining the effects of cannabis or psychoactive cannabinoid exposure on psychomotor performance in individuals using these substances solely for medical purposes, it is well known that exposure to such substances impairs psychomotor performance (118) and patients must be warned not to drive or operate complex machinery after smoking or eating cannabis or consuming psychoactive cannabinoid medications (e.g. dronabinol, nabilone, nabiximols).

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 (953). A "moderate" dose (21 mg of THC) was associated with impairments in motor and perceptual skills necessary for safe driving (954). In one study, performance impairment appeared to be less significant among heavy cannabis users compared to occasional users, potentially because of the development of tolerance or compensatory behaviour (169). 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 (955,956). Others disagree with this assertion ((957) and also see (176)).

A recent double-blind, placebo-controlled, randomized, three-way, crossover design study suggested that administration of dronabinol dose-dependently impaired driving performance in both occasional (defined as using a cannabinoid between 5 and 36 times per year) and heavy cannabis users (defined as using 1 - 3 joints per day, > 160 times per year) (958). However, the magnitude of the impairment appeared to be less in heavy users, possibly due to tolerance (958). The authors indicate that driving impairments after dronabinol were of clinical relevance and comparable to drivers operating their vehicles at a blood-alcohol concentration of greater than 0.8 mg/mL (0.08 g%) (958). Approximately 25% of the "heavy users" demonstrated impairment equivalent to, or worse than, that reported for drivers with a blood-alcohol concentration of 0.5 mg/mL (0.05 g%). Driving impairments after dronabinol use were evident even though THC plasma concentrations were relatively low (varying between 2 and 10 ng/mL) (175,958).

A recent case-control study estimating accident risk for a variety of substances including alcohol, medicines, and illegal drugs found that the odds ratio for accident risk for all the THC concentrations measured (1 to > 5 ng/mL) was statistically significant (959). At whole-blood concentrations of ≥ 2 ng/mL THC, the risk of having an accident was significantly increased (959). One study found that the risk of responsibility for fatal traffic crashes, while driving under the influence of cannabis, increased with increasing blood concentrations of THC such that there was a significant dose-effect relationship between risk of responsibility for fatal traffic crashes and blood concentrations of THC. The study showed that the odds ratio of having a fatal crash increased from 2.18 if blood concentrations ranged between 0 and 1 ng/mL of THC, to 4.72 if blood THC concentrations were ≥ 5 ng/mL (960). The findings from this study further support the notion of a causal relationship between cannabis use and crashes (960). Another study suggested that drivers who were judged (by a police physician) as being impaired had higher blood THC concentrations than drivers judged not to be impaired (median: 2.5 ng/mL vs. 1.9 ng/mL) (961). Using a binary logistic regression model, the odds ratio for being judged impaired appeared to increase with increasing drug concentrations from 2.9 ng/mL onwards (961). Serum THC concentrations between 2 and 5 ng/mL have been identified as a threshold above which THC-induced impairment of skills related to driving become apparent (133,959). Performance impairment

after cannabis intake was reported to be highest during the first hour after smoking, and between 1 - 2 h after oral intake, and declining after 3 - 4 h (or longer in the case of oral ingestion) (862,961).

A recent meta-analysis of observational studies examining acute cannabis consumption and motor vehicle collision risk reported that driving under the influence of cannabis was associated with a significantly increased risk of motor vehicle collisions compared with unimpaired driving, with an odds ratio of 1.92 (95% Confidence Interval = 1.35 - 2.73; $p = 0.0003$) (175). Collision risk estimates were higher in case-control studies and studies of fatal collisions, than in culpability studies and studies of non-fatal collisions (175). It has been reported that individuals who drive within 1 h of using cannabis are nearly twice as likely to be involved in motor vehicle accidents as those who do not consume cannabis (954). For this meta-analysis, only observational studies with a control or comparison group, including cohort (historical prospective), case-control, and culpability designs were included, and experimental laboratory or simulator studies were excluded (175). Furthermore, only studies that assessed acute or recent cannabis use were examined. This meta-analysis supports the findings of other studies which suggest that cannabis use impairs the performance of the cognitive and motor tasks that are required for safe driving, thereby increasing the risk of collision (175). Although driving simulator studies have reported a dose-response effect, in which elevated concentrations of THC were associated with increased crash risk, dose-response effects could not be established in this study (175).

A double-blind, counter-balanced, placebo-controlled driving simulator study reported that driving performance was more impaired in subjects who co-consumed alcohol and low or high doses of THC by smoking cannabis cigarettes (176). The level of THC detected in the blood was higher when cannabis was consumed along with alcohol than when consumed alone (176). It also appeared that regular cannabis users displayed more driving errors than non-regular cannabis users (176).

A recent systematic review and meta-analysis concluded that, after adjusting for study quality, cannabis use was associated with a seven-fold estimated risk of being involved in a fatal accident, benzodiazepine use was associated with a two-fold estimated risk of a fatal accident, and opiate use with a three-fold estimated risk of a fatal accident (177). In contrast, cannabis use was associated with a 1.5-fold estimated risk of having an accident that only caused injury, benzodiazepine use was associated with a 0.71-fold estimated risk, whereas opiates were associated with a 21-fold estimated risk of having an accident that only caused injury (177).

7.7.3 Psychiatric effects

7.7.3.1 Acute psychotic reactions

Cannabis and cannabinoid use has been linked to episodes of acute psychosis in both regular and drug-naïve users (122,145,962). In one report, two healthy patients who had participated in a randomized controlled trial (RCT) measuring the effects of orally administered cannabinoids (including dronabinol or cannabis decoctions) on psychomotor performance displayed acute psychotic reactions following exposure to cannabis (145). 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 (140). 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 (963).

7.7.3.2 Anxiety, Depression and Bipolar Disorder

Anxiety and depression

Cannabis is known to cause an acute and short-lasting episode of anxiety, often resembling a panic attack; this is more often encountered in naïve cannabis users and those who consume higher doses of cannabis or THC (> 5 mg oral Δ^9-THC), and also when cannabis is consumed in novel or stressful environments (147,155). While clinical trials of cannabis, or oral Δ^9-THC, to treat anxiety or depression show either a lack of improvement or worsening of these conditions (964,965,966,967) there is some evidence that cannabis or cannabinoids may be useful in treating anxiety or depression secondary to other disorders (e.g. chronic pain, post-traumatic stress disorder). For more information on potential therapeutic uses of cannabis or cannabinoids to treat anxiety and depression, please consult section 4.8.5.1.

Research on the topic of cannabis and depression is relatively scarce and conflicting. A 2003 review reported that the co-morbidity level between heavy or problematic cannabis use and depression, in surveys of the general population, exceeds what would be expected by chance (968). 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 limitations in study design, as well as limitations in the ability to measure cannabis use, and limitations in the ability to measure depression were also highlighted. A U.S. study of adults using longitudinal national survey data (n = 8 759) found that the odds of developing depression in past-year cannabis users was 1.4 times higher than the odds of non-users developing depression (969). 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 (970). In contrast, another U.S. study based on the results of the National Epidemiological Survey on Alcohol and Related Conditions (n = 43 093) found that major depression was significantly associated with lifetime cannabis disorders and dependence (971). A 2007 study using data from the Netherlands Mental Health Survey and Incidence Study found a modest increased risk of a first depressive episode (Odds Ratio = 1.62; 1.06 - 2.48), after controlling for strong confounding factors (972). Of greater significance in this study was the strong increased risk of bipolar disorder (Odds Ratio = 4.98; 1.80 - 13.81) with cannabis use (see below for further information on cannabis and bipolar disorder). 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 that cannabis users had significantly higher rates of suicidal behaviours and depressive and anxious symptoms compared to non-users (973). Another study suggested a putative positive association between exposure to cannabis and protracted suicidal thoughts or attempts in young people, although the study suffered from a number of limitations (974).

Bipolar disorder

Cannabis is one of the most frequently abused drugs in people diagnosed with bipolar disorder (148,975,976,977,978). A number of studies have examined the relationship between cannabis use and bipolar disorder, its effect on disease course, and its effect on treatment compliance.

One three-year, prospective study involving 4 815 subjects attempted to determine if baseline cannabis use increased the risk for development of manic symptoms, if the association between cannabis use and mania was independent of the emergence of psychotic symptoms, and if baseline mania predicted cannabis use at follow-up (975). The authors found that cannabis use at baseline was associated with follow-up mania (Odds Ratio = 5.32, 95% Confidence Interval: 3.59, 7.89). After adjusting for confounding factors, the association persisted although it was reduced (Odds Ratio = 2.70, 95% Confidence Interval: 1.54, 4.75). The risk of developing manic symptoms appeared to increase with increased baseline frequency of cannabis use (975). The effect size was largest for those who used cannabis 3 - 4 days/week, followed by those who used daily and 1 - 2 days/week, and lastly for those who used 1 - 3 days/month (975). The authors reported that manic

symptoms at baseline did not predict cannabis use during follow-up. The results suggested that use of cannabis increased the risk of developing subsequent manic symptoms and that this effect was dose-dependent (975).

Another group of investigators conducted a five-year, prospective, cohort study examining three groups of patients: one where a cannabis use disorder preceded the onset of bipolar disorder, another where bipolar disorder preceded a cannabis use disorder, and one group with bipolar disorder only (976). The authors found that cannabis use was associated with more time in affective (manic or mixed) episodes and with rapid cycling, but a causal relationship between cannabis use and bipolar disorder could not be established (976).

A separate prospective study which followed a group of type I bipolar patients over a 10-year period, beginning from the onset of illness, concluded that there was a strong association between cannabis use and manic/hypomanic episodes or symptoms, and that substance abuse preceded or coincided with, but did not follow, exacerbations of affective illness (979).

A two-year, prospective, observational study on the outcome of pharmacological treatment of mania (the European Mania in Bipolar Longitudinal Evaluation of Medication (EMBLEM) study) followed 3 459 eligible in- and out-patients who were being treated for acute mania in bipolar disorder, assessing patients' current cannabis use as well as the influence of cannabis exposure on clinical and social treatment outcome measures (148). The study concluded that during a one-year treatment period, cannabis users exhibited less treatment compliance and higher levels of overall illness severity, mania, and psychosis compared to non-users (148). Cannabis users also reported experiencing less satisfaction with life (148).

A preliminary study found that patients diagnosed with bipolar disorder with psychotic features were significantly more likely to carry a functional polymorphism in the promoter region of the *5-HT* transporter gene and also have a diagnosis of cannabis abuse/dependence, compared to bipolar patients who did not exhibit psychotic symptoms (978). Genetic studies have also raised the possibility of a link between allelic variants of the cannabinoid receptor gene (*CNR1*) and susceptibility to mood disorders (980,981).

The influence of cannabis use on age at onset in both schizophrenia and bipolar disorder (with psychotic symptoms) has been studied using regression analysis (150). The authors of this study found that although cannabis and other substance use was more frequent in patients with schizophrenia than those diagnosed with bipolar disorder, cannabis use was nonetheless associated with a decrease in age at onset in both disorders (150). Cannabis use also preceded first hospitalization in the vast majority of cases (95.4%). Furthermore, the period of most intensive use ("several times per day") preceded first admission in 87.1% of the cases (150). In bipolar patients, cannabis use reduced age at onset by an average of nine years (150). In contrast, in schizophrenic patients, cannabis use reduced age at onset by an average of 1.5 years (150). No significant difference was noted in age at onset between male and female patients in either of the diagnostic groups (150).

Another study investigated which factors were associated with age at onset in bipolar disorder, and also examined the sequence of the onsets of excessive substance use and bipolar disorder (982). A total of 151 patients with bipolar disorder (type I and II) receiving psychiatric treatment participated in the study. The authors found that when compared with alcohol use, excessive cannabis use (defined as either meeting DSM-IV criteria for substance use disorder, or weekly use of cannabis over a period of at least four years) was associated with an earlier age at onset in both primary and secondary bipolar disorder, even after adjusting for possible confounders (982). In addition, the mean age at onset of excessive cannabis use preceded the age at onset of bipolar disease; this was reversed in the alcohol group (982).

One study reported that when compared with controls, patients with bipolar disorder were almost seven times (95% Confidence Interval: 5.41 - 8.52) more likely to report a lifetime history of cannabis use (977). Furthermore, this association appeared to be gender-independent. Those patients who used cannabis after, or in tandem with, their onset of bipolar symptoms had a lower

age at onset of the disorder (17.5 vs. 21.5 yrs) (977). Furthermore, those who used cannabis prior to the onset of a bipolar disease episode were 1.75 times (95% Confidence Interval: 1.05 - 2.91) more likely to report disability attributable to bipolar disorder (977).

Lastly, a retrospective analysis of a large cohort of bipolar I subjects, with or without a history of a cannabis use disorder, reported that bipolar patients with a cannabis use disorder had similar age at onset as patients without such a substance use disorder (983). However, patients with a cannabis use disorder were more likely to have experienced psychosis at some time during the course of their illness compared to patients who never met the criteria for the disorder (983).

7.7.3.3 Schizophrenia and psychosis

The endocannabinoid system has been implicated in the pathogenesis of schizophrenia and psychosis (please see section 4.8.5.5 for more information). Individuals with schizophrenia, or with a family history of this disorder, are likely to be at greater risk of suffering adverse psychiatric effects as a result of using cannabis or psychoactive cannabinoids such as Δ^9-THC (152). Heavy cannabis use can aggravate psychotic symptoms and cause more relapses, and those individuals who use cannabis are at an increased risk of a poor prognosis (118,138,984,985). 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 cannabis exposure (986). A cohort study of over 1 000 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 (987). The relationship between cannabis use and psychotic symptoms was also studied in a cohort of 2 437 young people (ages 14 - 24 yrs) who had greater than average pre-disposition for psychosis, and who had first used cannabis during adolescence (146). 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 pre-disposition for psychosis. 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 (Odds Ratio = 1.41) (141). Furthermore, the findings appeared to show a dose-related effect, with greater risk to individuals who used cannabis most frequently (Odds Ratio = 2.09) (149,150).

In one study, the relationship between age at onset of psychosis and other clinical characteristics in a sample of well-characterized patients diagnosed with bipolar disorder with psychosis, schizoaffective disorder, or schizophrenia, has been investigated (149). The study concluded that lifetime cannabis abuse/dependence was associated with a significantly earlier age at onset of psychosis (3.1 years, 95% Confidence Interval: 1.4 - 4.8) (149). Furthermore, among those patients with lifetime cannabis abuse/dependence, the age at onset of cannabis abuse/dependence preceded the onset of psychotic illness by almost another three years (149). However, patients who had a lifetime cannabis abuse/dependence diagnosis and a lifetime alcohol abuse/dependence diagnosis had a significantly later age at onset of psychosis (149).

Another study looked at the influence of cannabis use on age at onset in both schizophrenia and bipolar disorder (with psychotic symptoms) using regression analysis (150). The authors of this study found that although cannabis and other substance use was more frequent in patients with schizophrenia than those diagnosed with bipolar disorder, cannabis use was nonetheless associated with a decrease in age at onset in both disorders (150). Cannabis use also preceded first hospitalization in the vast majority of cases (95.4%) and furthermore, the period of most intensive use ("several times per day") preceded first admission in 87.1% of the cases (150). In bipolar patients, cannabis use reduced age at onset by an average of nine years (150). In contrast, in schizophrenic patients, cannabis use reduced age at onset by an average of 1.5 years (150). No significant difference was noted in age at onset between male and female patients in either of the diagnostic groups (150).

Although cannabis use increases the risk of psychosis, it is only one factor in a larger constellation of contributing factors (988).

Genetic factors

A number of studies have investigated the influence of potential genetic factors in the development of psychosis and schizophrenia, and more specifically as a function of interaction with cannabis use. Some studies have focused on the role of genetic polymorphisms at the catechol-O-methyltransferase gene (*COMT*) (686,687,688,689,690), while others have focused on polymorphisms at the *AKT1* gene (691,692,693), or the brain-derived neurotrophic factor (*BDNF*) gene (989).

Schizophrenia and the Catechol-O-Methyltransferase gene

Catechol-O-methyltransferase (COMT) regulates the breakdown of catecholamines, including neurotransmitters such as dopamine, epinephrine, and norepinephrine (690). A missense mutation at codon 158 in the *COMT* gene, causing a substitution to the methionine (Met) at the positional valine (Val) (Val158Met), results in an enzyme with decreased activity and correspondingly slower dopamine catabolism (990,991). Changes in dopaminergic tone and signaling are known to affect neurophysiological function, and these changes have been implicated in the pathophysiology of schizophrenia (992). Although a large-scale association study and meta-analysis has failed to find a strong association between the Val158Met *COMT* polymorphism and vulnerability to schizophrenia (993), evidence gathered from convergent functional genomic data nevertheless implicates the *COMT* gene (as well as the *CNR1* and *2* genes) in the pathophysiology of schizophrenia (994). Caspi et al. (686) followed an epidemiological birth cohort of 1 037 children longitudinally across the first three decades of life. They concluded that the *COMT* Val/Val homozygous genotype interacted with adolescent-onset cannabis use, but not adult-onset use, to predict the emergence of adult psychosis (686). Subsequent studies confirmed and extended these findings (687,688,689,690,693). Carriers of the Val allele were most sensitive to Δ^9-THC-induced psychotic experiences (especially if they scored highly on a psychosis liability assessment), and were also more sensitive to the Δ^9-THC-induced memory and attention impairments compared to carriers of the Met allele (687). Homozygous carriers of the Val allele, but not subjects with the homozygous Met genotype, showed an increase in the incidence of hallucinations after cannabis exposure, but this was conditional on prior psychometric evidence of psychosis liability (688). Those patients who were Val/Met heterozygous also appeared to be more sensitive to the effects of cannabis than Met homozygotes, but less sensitive than Val homozygotes (688). Another study suggested that cannabis use could reduce the (protective) delay effect of the *COMT* Met allele in influencing the age of onset of psychosis (689). These findings were supported, and extended, by a subsequent study which showed that those who started using cannabis earlier had an earlier age at onset of psychiatric disorders, and that carriers of the Val homozygous genotype had an earlier age of onset of psychosis compared to Met carriers (690). The authors of this study concluded that gene-environment interaction (i.e. the combination of the *COMT* Val to Met polymorphism and cannabis use) may modulate the emergence of psychosis in adolescents (690). Taken together, these studies also suggest the presence of a gene-dosage effect, with increasing disease risk among Val/Val homozygotes, moderate risk in Val/Met heterozygotes, and less risk among Met/Met homozygotes.

Schizophrenia and the AKT1 gene

Other studies have focused on the role of *AKT1*, a gene that encodes a protein kinase involved in the dopamine and cannabinoid receptor signaling cascades, and which is involved in regulating cellular metabolism, cell stress, cell-cycle regulation, and apoptosis as well as regulating neuronal cell size and survival (691). In one study, the authors found evidence of a gene-environment interaction between a single nucleotide polymorphism in the *AKT1* gene (rs2494732, C/C homozygous polymorphism) and cannabis use (692). Individuals with the C/C homozygous polymorphism had an approximately two-fold increased risk of being diagnosed with a psychotic disorder after having used cannabis either daily or weekly (692). In contrast, C/T heterozygous individuals had only a slightly increased risk of developing cannabis-related psychosis compared to T/T homozygotes, which served as the controls (692). In another study by the same group, individuals with the rs2494732 C/C homozygous polymorphism exhibited a deficit in sustained attention, but not in verbal memory, even in the absence of current cannabis use (691).

Schizophrenia and the Brain-Derived Neurotrophic Factor gene

One study found that cannabis use, before diagnosis of schizophrenia, was associated with a decrease in the age at onset of a psychotic disorder, decreasing the age at first admission by almost three years (989). Furthermore, a dose-dependent association between cannabis use and age at onset of psychotic symptoms was found, with an earlier onset of psychotic disorder in heavier users (989). A significant association between a younger age of first cannabis use and an earlier onset of psychotic disorder was also found, even after controlling for possible confounders (989). In that study, cannabis use independently predicted age at onset of a psychotic disorder in male patients, whereas in female patients cannabis use was only associated with age at onset of psychotic disorder in those who carried a Met allele mutation in the gene for brain-derived neurotrophic factor (*BDNF*). Female carriers of the mutant Met allele presented with psychotic symptoms seven years earlier than female patients who did not use cannabis and who had a *BDNF* Val/Val genotype (989).

In conclusion, given the evidence suggesting a strong genetic component in the modulation of psychosis, and especially psychosis or schizophrenia precipitated by cannabis use, the taking of a thorough patient medical history, especially one which includes a psychiatric history/evaluation, would be very valuable in determining whether cannabis/cannabinoids represent a sensible and viable therapeutic option.

7.7.3.4 Amotivational syndrome

The term "amotivational syndrome" is generally used to qualify people who exhibit apathy, lack of motivation, social withdrawal, narrowing of interests, lethargy, impaired memory, impaired concentration, disturbed judgement, and impaired occupational achievement (995).

Some investigators suggest that heavy, chronic use of cannabis is linked to the development of such a syndrome (995); de-intoxication results in resolution of symptoms (152,996). Other investigators have not found such a causal relationship (995,997).

8.0 Overdose/Toxicity

LD_{50} values for rats administered single oral doses of THC, or crude cannabis extract, are approximately 1000 mg/kg (998). Dogs and monkeys are able to tolerate significantly higher oral doses of THC, or cannabis extract, of 3000 mg/kg (or greater in certain cases) (998). The estimated human lethal dose of intravenous THC is 30 mg/kg (2100 mg/70 kg) (174), although there has been no documented evidence of death exclusively attributable to cannabis overdose to date. Significant CNS symptoms are observed with oral doses of 0.4 mg/kg dronabinol (Marinol®) (174). Cannabis and THC often produce unwanted physical effects, typically dizziness, sedation, intoxication, transient impairment of sensory and perceptual functions, clumsiness, dry mouth, lowered blood pressure, or increased heart rate (174,999). These adverse effects are generally tolerable and not unlike those seen with other medications (118). The rare acute complications (e.g. panic attacks, psychosis, convulsions, etc.) that present to hospital Emergency Departments can be managed with conservative measures, such as reassurance in a quiet environment, and administration of benzodiazepines, if required (1000). As is stated in the case of overdose with Marinol® (174), the signs and symptoms observed with smoked or ingested cannabis are an extension of the psychotomimetic and physiologic effects of THC. Individuals experiencing psychotic reactions should stop using cannabis or cannabinoids immediately and seek prompt medical/psychiatric attention.

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