INFORMATION FOR HEALTH CARE PROFESSIONALS

Cannabis (marihuana, marijuana) and the cannabinoids

Dried or fresh plant and oil administration by ingestion or other means
Psychoactive agent

Government of Canada Gouvernement du Canada

Canada

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RENSEIGNEMENTS DESTINÉS AUX PROFESSIONNELS DE LA SANTÉ
Le cannabis (marihuana, marijuana) et les cannabinoïdes
Plante séchée ou fraîche et huile destinées à l'administration par ingestion ou par d'autres moyens
Agent pyschoactif

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Cannabis (marihuana, marijuana) and the cannabinoids
Dried or fresh plant and oil for administration by ingestion or other means
Psychoactive agent

This document has been prepared by the Cannabis Legalization and Regulation Branch at Health Canada to provide information on the use of cannabis (marihuana) and cannabinoids for medical purposes. This document is a summary of peer-reviewed literature and international reviews concerning potential therapeutic uses and harmful effects of cannabis and cannabinoids. It is not meant to be comprehensive and should be used as a complement to other reliable sources of information. This document is not a systematic review or meta-analysis of the literature and has not rigorously evaluated the quality and weight of the available evidence nor has it graded the level of evidence. 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 should not be construed as expressing conclusions or opinions from Health Canada about the appropriate use of cannabis (marihuana) or cannabinoids for medical purposes.

Cannabis is not an approved therapeutic product, unless a specific cannabis product has been issued a drug identification number (DIN) and a notice of compliance (NOC). The provision of this information should not be interpreted as an endorsement of the use of this product, or cannabis and cannabinoids generally, by Health Canada.

Prepared by Health Canada

Date of latest version: Spring 2018

Reporting Adverse Reactions to Cannabis (marihuana, marijuana) Products

Reporting adverse reactions associated with the use of cannabis and cannabis products is important in gathering much needed information about the potential harms of cannabis and cannabis products for medical purposes. When reporting adverse reactions, please provide as much complete information as possible including the name of the licensed producer, the product brand name, the strain name, and the lot number of the product used in addition to all other information available for input in the adverse reaction reporting form. Providing Health Canada with as much complete information as possible about the adverse reaction will help Health Canada with any follow-ups or actions that may be required.

Any suspected adverse reactions associated with the use of cannabis and cannabis products (dried, oils, fresh) for medical purposes should be reported to the Canada Vigilance Program by one of the following three ways:

1. **Report online**
2. **Call toll-free at 1-866-234-2345**
3. **Complete a Canada Vigilance Reporting Form and:**
   - **Fax toll-free to 1-866-678-6789, or**
   - **Mail to:**
     Canada Vigilance Program
     Health Canada
     Postal Locator 0701D
     Ottawa, Ontario K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site.

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2-AG: 2-arachidonoylglycerol
5-ASA: 5-aminosalicylic acid
5-HT: 5-hydroxytryptamine
2-OG: 2-oleoylglycerol
AA: arachidonic acid
AB: Alberta
ACCESS: AIDS Care Cohort to evaluate Exposure to Survival Services
ACE: angiotensin-converting enzyme
ACMPR: Access to Cannabis for Medical Purposes Regulations
ACTH: adrenocorticotropic hormone
AD: Alzheimer's disease
AED: anandamide
AIDS: acquired immune deficiency syndrome
AKT1: AKT Serine/Threonine Kinase 1
ALS: amyotrophic lateral sclerosis
ALSPAC: Avon Longitudinal Study of Parents and Children
ALT: alanine transaminase
AMP: adenosine monophosphate
AOR: adjusted odds ratio
ApoE: apolipoprotein E
APP: amyloid precursor protein
APRI: AST-to-platelet ratio index
ART: anti-retroviral therapy
AST: aspartate transaminase
AUC: area-under-the-curve
AUC_{12}: 12-hour AUC
Aβ: amyloid-beta
b.i.d.: *bis in die* (i.e. twice per day)
BAC: blood alcohol concentration
BC: British Columbia
BCOS: Bipolar Comprehensive Outcomes Study
BDNF: brain-derived neurotrophic factor
BDS: botanical drug substance
BHO: butane hash oil
BMI: body mass index
BPI: Brief Pain Inventory
Ca^{2+}: calcium
CADUMS: Canadian Alcohol and Drug Use Monitoring Survey
CAMPS: Cannabis Access for Medical Purposes Survey
CAMS: Cannabis in Multiple Sclerosis
CAPS: Clinician-Administered PTSD Scale
CARDIA: Coronary Artery Risk Development In young Adults
CB: cannabinoid
CBC: cannabichromene
CBD: cannabidiol
CBDA: cannabidiolic acid
CBDV: cannabidivarin
CBG: cannabigerol
CBN: cannabinol
CCL: chemokine (C-C motif) ligand
CDAI: Crohn's disease activity index
CDKL5: cyclin-dependent kinase-like 5 gene
CHS: cannabis hyperemesis syndrome
CI: confidence interval
CINV: chemotherapy-induced nausea and vomiting
CGI-I: clinical global impression improvement

CGI-S: clinical global impression scale
cMAS: combined modified Ashworth score
Cmax: Maximal concentration of a drug in the blood
CNR1: cannabinoid receptor 1
CNR2: cannabinoid receptor 2
CNS: central nervous system
COMT: catechol-O-methyltransferase
COX: cyclo-oxygenase
CRP: C-reactive protein
CRPS: complex regional pain syndrome
CSF: cerebrospinal fluid
CUD: cannabis use disorder
CUPID: Cannabinoid Use in Progressive Inflammatory Brain Disease
CYP: cytochrome P450
D: duration of action
DAG: diacylglycerol
DAGL: diacylglycerol lipase
DAT1: dopamine active transporter 1
DIO: diet-induced obesity
DNA: deoxyribonucleic acid
DNBS: dinitrobenzene sulfonic acid
DSM-5: diagnostic and statistical manual of mental disorders (fifth edition)
DSM-IV: diagnostic and statistical manual of mental disorders (fourth edition)
DUIA: driving under the influence of alcohol
DUIC: driving under the influence of cannabis
ECS: endocannabinoid system
ED_{50}: median effective dose
EDSP: Early Developmental Stages of Psychopathology
EDSS: expanded disability status scale
EEG: electroencephalogram
e.g.: for example
EMBLEM: European Mania in Bipolar Longitudinal Evaluation of Medication
EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, Core Module
EQ-5D: EuroQoL five dimensions questionnaire
ESM: experience sampling methodology
ETA: ethanolamine
FAACT: Functional Assessment of Anorexia-Cachexia Therapy
FAAH: fatty acid amide hydrolase
FEV_1: forced expiratory volume in one second
fMRI: functional magnetic resonance imaging
FSH: follicle stimulating hormone
FVC: forced vital capacity
g: gram
GABA: gamma-aminobutyric acid
GAD: generalized anxiety disorder
GI: gastrointestinal
GnRH: gonadotropin-releasing hormone
GPR55: G protein-coupled receptor 55
GRADE: Grading of Recommendations, Assessment, Development and Evaluation
GVHD: graft-versus-host disease
h: hour
H^1-MRS: proton magnetic resonance spectroscopy
HD: Huntington’s disease
HDL: high density lipoprotein
HIV: human immunodeficiency virus
HMG-CoA: 3-hydroxy-3-methyl-glutaryl-coenzyme A
HMO: health maintenance organization
HOMA-IR: homeostatic model assessment of insulin resistance

HPA: hypothalamic-pituitary-adrenal
HPO: hypothalamic-pituitary-ovarian
HRQoL: health-related quality of life
I.M.: intramuscular
I.P.: intraperitoneal
I.V.: intravenous
IBD: inflammatory bowel disease
IBS: irritable bowel syndrome
IBS-A: alternating pattern (alternation constipation/diarrhea) IBS
IBS-C: constipation-predominant IBS
IBS-D: diarrhea-predominant IBS
IC_{50}: median inhibitory concentration
ICAM-1: intercellular adhesion molecule-1
ICD: International Classification of Diseases
ICM: inner cell mass
IFN: interferon
IL: interleukin
IND: investigational new drug
iNOS: inducible nitric oxide synthase
IOP: intraocular pressure
IQ: intelligence quotient
IQR: interquartile range
IRR: incident rate ratio
K^+: potassium
kg: kilogram
L: liter
LCT: lipid long-chain triglyceride
LD_{50}: median lethal dose
LDL: low density lipoprotein
LH: luteinizing hormone
LOX: lipo-oxygenase
MAGL: monoacylglycerol lipase
MB: Manitoba
Met: methionine
mg: milligram
min: minute
miRNA: micro ribonucleic acid
mL: milliliter
MMP: matrix metalloproteinase
MOVE 2: Mobility Improvement in MS-Induced Spasticity Study
mRNA: messenger ribonucleic acid
MS: multiple sclerosis
MSIS-29: MS Impact Scale 29
MUSEC: Multiple Sclerosis and Extract of Cannabis trial
N/A: not applicable
Na^+: sodium
NAFLD: non-alcoholic fatty liver disease
NAPE: N-arachidonoylphosphatidylethanolamine
NASEM: National Academy of Sciences, Engineering and Medicine
NB: New Brunswick
NCS: National Comorbidity Survey
NCS-R: National Comorbidity Survey-Replication
NEMESIS: Netherlands Mental Health Survey and Incidence Study
NESARC: National Epidemiological Survey on Alcohol and Related Conditions
ng: nanogram
NHANES: National Health and Nutrition Examination Survey
NK: natural killer
NK-1: neurokinin 1

NL: Newfoundland and Labrador
nM: nanomolar
NMDA: N-methyl-D-aspartic acid
nmol: nanomole
NNT: number needed to treat
NRG1: neuregulin 1
NRS: numerical rating scale
NRS-PI: numerical rating scale for pain intensity
NS: Nova Scotia
NSAIDs: nonsteroidal anti-inflammatory drugs
NSDUH: National Survey on Drug Use and Health
NT: Northwest Territories
NU: Nunavut
O: onset of effects
OA: osteoarthritis
OEA: oleoylethanolamide
ON: Ontario
OR: odds ratio
P: peak effects
PE: Prince Edward Island
P.O.: oral administration
PD: Parkinson's disease
PDQ-39: 39-Item Parkinson Disease Questionnaire
PEA: palmitoylethanolamide
PLD: phospholipase-D
pNRS: pain numerical rating score
PPAR: peroxisome proliferator-activated receptor
PRISMA: Preferred Reporting Items for Sytematic Reviews and Meta-Analyses
PTSD: post-traumatic stress disorder
PWID: people who inject drugs
QC: Quebec
q.i.d.: *quater in die* (i.e. four times per day)
QoL: quality of life
RA: rheumatoid arthritis
RCT: randomized controlled trial
REM: rapid eye movement
RNA: ribonucleic acid
Rx: prescription
s: second
SAFTEE: Systematic Assessment of Treatment Emergent Events
s.c.: subcutaneous
SCI: spinal cord injury
SD: standard deviation
SDLP: standard deviation of lateral position
SF-36: 36-Item Short Form Health Survey
SIBDQ: short IBD questionnaire
SIV: simian immunodeficiency virus
SK: Saskatchewan
SNP: single nucleotide polymorphism
sNRS: subjective numerical rating spasticity scale
S-TOPS: Short-Form Treatment Outcomes in Pain Survey
SYS: Saguenay Youth Study
t.i.d.: *ter in die* (i.e. three times per day)
TGCT: testicular germ cell tumours
THC: delta-9-tetrahydrocannabinol
THCA: tetrahydrocannabinolic acid
THCV: tetrahydrocannabivarin
TIA: transient ischemic attack

Tmax: Time to maximal blood concentration of a drug
TNBS: trinitrobenzene sulfonic acid
TNF: tumor necrosis factor
TRH: thyrotropin-releasing hormone
TRP: transient receptor potential
TRPV1: transient receptor potential vanilloid channel 1
TS: Tourette's syndrome
TWSTRS: Toronto Western Spasmodic Torticollis Rating Scale
U.K.: United Kingdom
UPDRS: Unified Parkinson's Disease Rating Scale
Val: valine
VAS: visual analogue scale
VCAM-1: vascular cellular adhesion molecule-1
w/w: weight/weight
WHO: World Health Organization
YT: Yukon
Δ^9-THC: delta-9-tetrahydrocannabinol
µg: microgram
µM: micromolar

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Overview of Summary Statements

The following bullet-point statements are meant to summarize the content found within sections 4.0 (Potential Therapeutic Uses) and 7.0 (Adverse Effects) and their respective subsections. The bullet-point statements can also be found in their respective sections and sub-sections in the body of the document itself. Note: most, but not all, clinical studies of cannabis (experimental or therapeutic) have been conducted with dried cannabis containing more THC than CBD and typically, but not always, with lower-potency THC (< 9% THC). Furthermore, the majority of the clinical studies of cannabis (experimental or therapeutic) have administered dried cannabis by smoking. Lastly, the findings from clinical studies of cannabis for therapeutic purposes may not be applicable to other chemotypes of cannabis or other cannabis products with different THC and CBD amounts and ratios.

4.0 Potential Therapeutic Uses

4.1 Palliative care

- The evidence thus far from some observational studies and clinical studies suggests that cannabis (limited evidence) and prescription cannabinoids (e.g. dronabinol, nabilone, or nabiximols) may be useful in alleviating a wide variety of single or co-occurring symptoms often encountered in the palliative care setting.
- These symptoms may include, but are not limited to, intractable nausea and vomiting associated with chemotherapy or radiotherapy, anorexia/cachexia, severe intractable pain, severe depressed mood and anxiety, and insomnia.
- A limited number of observational studies suggest that the use of cannabinoids for palliative care may also potentially be associated with a decrease in the number of some medications used by this patient population.

4.2 Quality of life

- The available clinical studies report mixed effects of cannabis and prescription cannabinoids on measures of quality of life (QoL) for a variety of different disorders.

4.3 Chemotherapy-induced nausea and vomiting

- Pre-clinical studies show that certain cannabinoids (THC, CBD, THCV, CBDV) and cannabinoid acids (THCA and CBDA) suppress acute nausea and vomiting as well as anticipatory nausea.
- Clinical studies suggest that certain cannabinoids and cannabis (limited evidence) use may provide relief from chemotherapy-induced nausea and vomiting (CINV).

4.4 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 available evidence from human clinical studies suggests that cannabis (limited evidence) and dronabinol may increase appetite and caloric intake, and promote weight gain in patients with HIV/AIDS.
- However the evidence for dronabinol is mixed and effects modest for patients with cancer and weak for patients with anorexia nervosa.

4.5 Multiple sclerosis, amyotrophic lateral sclerosis, spinal cord injury and disease

- Evidence from pre-clinical studies suggests THC, CBD and nabiximols improve multiple sclerosis (MS) associated symptoms of tremor, spasticity and inflammation.
- The available evidence from clinical studies suggest cannabis (limited evidence) and certain cannabinoids (dronabinol, nabiximols, THC/CBD) are associated with some measure of improvement in symptoms encountered in MS and spinal cord injury (SCI) including spasticity, spasms, pain, sleep and symptoms of bladder dysfunction.
- Very limited evidence from pre-clinical studies suggest that certain cannabinoids modestly delay disease progression and prolong survival in animal models of amyotrophic lateral sclerosis (ALS), while the results from a very limited number of clinical studies are mixed.

4.6 Epilepsy

- Anecdotal evidence suggests an anti-epileptic effect of cannabis (THC- and CBD-predominant strains).
- The available evidence from pre-clinical studies suggests certain cannabinoids (CBD) may have anti-epileptiform and anti-convulsive properties, whereas CB_1R agonists (THC) may have either pro- or anti-epileptic properties.
- However, the clinical evidence for an anti-epileptic effect of cannabis is weaker, but emerging, and requires further study.
- Evidence from clinical studies with Epidiolex® (oral CBD) suggest efficacy and tolerability of Epidiolex® for drug-resistant seizures in treatment-resistant Dravet syndrome or Lennox-Gastaut syndrome.

- Evidence from observational studies suggest an association between CBD (in herbal and oil preparations) and a reduction in seizure frequency as well as an increase in quality of life among adolescents with rare and serious forms of drug-resistant epilepsy.
- Epidiolex® has received FDA approval (in June 2018) for use in patients 2 years of age and older to treat treatment-resistant seizures associated with Dravet syndrome and Lennox-Gastaut syndrome.

4.7 Pain

4.7.1 Acute pain

- Pre-clinical studies suggest that certain cannabinoids can block the response to experimentally-induced acute pain in animal models.
- The results from clinical studies with smoked cannabis, oral THC, cannabis extract, and nabilone in experimentally-induced acute pain in healthy human volunteers are limited and mixed and suggest a dose-dependent effect in some cases, with lower doses of THC having an analgesic effect and higher doses having a hyperalgesic effect.
- Clinical studies of certain cannabinoids (nabilone, oral THC, levonontradol, AZD1940, GW842166) for post-operative pain suggest a lack of efficacy.

4.7.2 Chronic pain

4.7.2.1 Experimentally-induced inflammatory and chronic neuropathic pain

- Endocannabinoids, THC, CBD, nabilone and certain synthetic cannabinoids have all been identified as having an anti-nociceptive effect in animal models of chronic pain (inflammatory and neuropathic).

4.7.2.2. Neuropathic pain and chronic non-cancer pain in humans

- A few studies that have used experimental methods having predictive validity for pharmacotherapies used to alleviate chronic pain, have reported an analgesic effect of smoked cannabis.
- Furthermore, there is more consistent evidence of the efficacy of cannabinoids (smoked/vapourized cannabis, nabiximols, dronabinol) in treating chronic pain of various etiologies, especially in cases where conventional treatments have been tried and have failed.

4.7.2.3 Cancer pain

- The limited available clinical evidence with certain cannabinoids (dronabinol, nabiximols) suggests a modest analgesic effect of dronabinol and a modest and mixed analgesic effect of nabiximols on cancer pain.

4.7.2.4 "Opioid-sparing" effects and cannabinoid-opioid synergy

- While pre-clinical and case studies suggest an "opioid-sparing" effect of certain cannabinoids, epidemiological and clinical studies with oral THC and nabiximols are mixed.
- Observational studies suggest an association between U.S. states with laws permitting access to cannabis (for medical and non-medical purposes) and lowered rates of prescribed opioids and opioid-associated mortality.

4.7.2.5 Headache and migraine

- The evidence supporting using cannabis/certain cannabinoids to treat headache and migraine is very limited and mixed.

4.8. Arthritides and musculoskeletal disorders

- The evidence from pre-clinical studies suggests stimulation of CB_1 and CB_2 receptors alleviates symptoms of osteoarthritis (OA), and THC and CBD alleviate symptoms of rheumatoid arthritis (RA).
- The evidence from clinical studies is very limited, with a modest effect of nabiximols for RA.
- There are no clinical studies of cannabis for fibromyalgia, and the limited clinical evidence with dronabinol and nabilone suggest a modest effect on decreasing pain and anxiety, and improving sleep.
- The role of cannabinoids in osteoporosis has only been investigated pre-clinically and is complex and conflicting.

4.9 Other diseases and symptoms

4.9.1 Movement disorders

4.9.1.1 Dystonia

- Evidence from limited pre-clinical studies suggests that a synthetic CB_1 and CB_2 receptor agonist may alleviate dystonia-like symptoms, and CBD delays dystonia progression.
- Evidence from a limited number of case studies and small placebo-controlled or open-label clinical trials suggests improvement in symptoms of dystonia with inhaled cannabis, mixed effects of oral THC, improvement in symptoms of dystonia with oral CBD, and lack of effect of nabilone on symptoms of dystonia.

4.9.1.2 Huntington's disease

- Evidence from pre-clinical studies reports mixed results with THC on Huntington's disease (HD)-like symptoms.
- Limited evidence from case studies and small clinical trials is mixed and suggests a lack of effect with CBD, nabilone and nabiximols, and a limited improvement in HD symptoms with smoked cannabis.

4.9.1.3 Parkinson's disease

- The evidence from a limited number of pre-clinical, case, clinical and observational studies of certain cannabinoids for symptoms of Parkinson's disease (PD) is mixed.
- One case study of smoked cannabis suggests no effect while an observational study of smoked cannabis suggests improvement in symptoms.
- One small clinical study of nabilone suggests improvement in symptoms, while another clinical study of an oral cannabis extract (THC/CBD) and a clinical study with CBD suggest no improvement in symptoms.

4.9.1.4 Tourette's syndrome

- The limited evidence from small clinical studies suggests that oral THC improves certain symptoms of Tourette's syndrome (TS) (tics).

4.9.2 Glaucoma

- The limited evidence from small clinical studies suggests oral administration of THC reduces intra-ocular pressure (IOP) while oral administration of CBD may, in contrast, cause an increase in IOP.

4.9.3 Asthma

- The limited evidence from pre-clinical and clinical studies on the effect of aerosolized THC on asthmatic symptoms is mixed.
- Inhalation of lung irritants generated from smoking/vapourizing cannabis may worsen asthmatic symptoms.

4.9.5 Stress and psychiatric disorders

4.9.5.1 Anxiety and depression

- Evidence from pre-clinical and clinical studies suggests that THC exhibits biphasic effects on mood, with low doses of THC having anxiolytic and mood-elevating effects and high doses of THC having anxiogenic and mood-lowering effects.
- Limited evidence from a small number of clinical studies of THC-containing cannabis/certain prescription cannabinoids suggests that these drugs could improve symptoms of anxiety and depression in patients suffering from anxiety and/or depression secondary to certain chronic diseases (e.g. patients with HIV/AIDS, MS, and chronic neuropathic pain).
- Evidence from pre-clinical studies suggests that CBD exhibits anxiolytic effects in various animal models of anxiety, while limited evidence from clinical studies suggest CBD may have anxiolytic effects in an experimental model of social anxiety.
- Limited evidence from some observational studies also suggests that cannabis containing equal proportions of CBD and THC is associated with an attenuation of some perturbations in mood (anxiety/dejection) seen with THC-predominant cannabis in patients using cannabis for medical purposes.

4.9.5.2 Sleep disorders

- Human experimental data suggests cannabis and THC have a dose-dependent effect on sleep—low doses appear to decrease sleep onset latency and increase slow-wave sleep and total sleep time, while high doses appear to cause sleep disturbances.
- Limited evidence from clinical studies also suggest that certain cannabinoids (cannabis, nabilone, dronabinol, nabiximols) may improve sleep in patients with disturbances in sleep associated with certain chronic disease states.

4.9.5.3 Post-traumatic stress disorder

- Pre-clinical and human experimental studies suggest a role for certain cannabinoids in alleviating post-traumatic stress disorder (PTSD)-like symptoms.
- However, while limited evidence from short-term clinical studies suggests a potential for oral THC and nabilone to decrease certain symptoms of PTSD, there are no long-term clinical studies for these preparations or any clinical studies of smoked/vapourized cannabis for PTSD.
- Limited evidence from observational studies suggests an association between herbal cannabis use and persistent/high levels of PTSD symptom severity over time.
- There is limited evidence to suggest an association between PTSD and CUD.

4.9.5.4 Alcohol and opioid withdrawal symptoms (drug withdrawal symptoms/drug substitution)

- Pre-clinical studies suggest CB_1 receptor agonism (e.g. THC) may help increase the reinforcing properties of alcohol, increase alcohol consumption, and increase risk of relapse of alcohol use, as well as exacerbate alcohol withdrawal symptom severity.
- Pre-clinical studies suggest certain cannabinoids (e.g. THC) may alleviate opioid withdrawal symptoms.
- Evidence from observational studies suggests that cannabis use could help alleviate opioid withdrawal symptoms, but there is insufficient clinical evidence from which to draw any reliable conclusions.

4.9.5.5 Schizophrenia and psychosis

- Significant evidence from pre-clinical, clinical and epidemiological studies supports an association between cannabis (especially THC-predominant cannabis) and THC, and an increased risk of psychosis and schizophrenia.
- Emerging evidence from pre-clinical, clinical and epidemiological studies suggests CBD may attenuate THC-induced psychosis.

4.9.6 Alzheimer's disease and dementia

- Pre-clinical studies suggest that THC and CBD may protect against excitotoxicity, oxidative stress and inflammation in animal models of Alzheimer's disease (AD).
- Limited case, clinical and observational studies suggest that oral THC and nabilone are associated with improvement in a number of symptoms associated with AD (e.g. nocturnal motor activity, disturbed behaviour, sleep, agitation, resistiveness).

4.9.7 Inflammation

4.9.7.1 Inflammatory skin diseases (dermatitis, psoriasis, pruritus)

- The results from pre-clinical, clinical and case studies on the role of certain cannabinoids in the modulation of inflammatory skin diseases are mixed.
- Some clinical and prospective case series studies suggest a protective role for certain cannabinoids (THC, CBD, HU-210), while others suggest a harmful role (cannabis, THC, CBN).

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

4.9.8.1 Irritable bowel syndrome

- Pre-clinical studies in animal models of irritable bowel syndrome (IBS) suggest that certain synthetic cannabinoid receptor agonists inhibit colorectal distension-induced pain responses and slow GI transit.
- Experimental clinical studies with healthy volunteers reported dose- and sex-dependent effects on various measures of GI motility.
- Limited evidence from one small clinical study with dronabinol for symptoms of IBS suggests dronabinol may increase colonic compliance and decrease colonic motility index in female patients with diarrhea-predominant IBS (IBS-D) or

with alternating pattern (alternating constipation/diarrhea) IBS (IBS-A), while another small clinical study with dronabinol suggests a lack of effect on gastric, small bowel or colonic transit.

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

- Pre-clinical studies in animal models of inflammatory bowel disease (IBD) suggest that certain cannabinoids (synthetic CB_1 and CB_2 receptor agonists, THC, CBD, CBG, CBC, whole plant cannabis extract) may limit intestinal inflammation and disease severity to varying degrees.
- Evidence from observational studies suggests that patients use cannabis to alleviate symptoms of IBD.
- A very limited number of small clinical studies with patients having IBD and having failed conventional treatments reported improvement in a number of IBD-associated symptoms with smoked cannabis.

4.9.8.3 Diseases of the liver (hepatitis, fibrosis, steatosis, ischemia-reperfusion injury, hepatic encephalopathy)

- Pre-clinical studies suggest CB_1 receptor activation is detrimental in liver diseases (e.g. promotes steatosis, fibrosis); while CB_2 receptor activation appears to have some beneficial effects.
- Furthermore, pre-clinical studies also suggest that CBD, THCV and ultra-low doses of THC may have some protective effects in hepatic ischemia-reperfusion injury and hepatic encephalopathy.

4.9.8.4 Metabolic syndrome, obesity, diabetes

- Pre-clinical studies suggest acute CB_1 receptor activation results in increased fat synthesis and storage while chronic CB_1 receptor activation (or CB_1 receptor antagonism) results in weight loss and improvement in a variety of metabolic indicators.
- Observational studies suggest an association between chronic cannabis use and an improved metabolic profile, while pre-clinical and very limited clinical evidence suggests a potential beneficial effect of THCV on glycemic control (in patients with type II diabetes).

4.9.8.5 Diseases of the pancreas (diabetes, pancreatitis)

- Pre-clinical studies in experimental animal models of certain cannabinoids in the treatment of acute or chronic pancreatitis are limited and conflicting.
- Limited evidence from case studies suggests an association between acute episodes of heavy cannabis use and acute pancreatitis.
- Limited observational studies suggest an association between chronic cannabis use and lower incidence of diabetes mellitus.
- One small clinical study reported that orally administered THC did not alleviate abdominal pain associated with chronic pancreatitis.

4.9.9 Anti-neoplastic properties

- Pre-clinical studies suggest that certain cannabinoids (THC, CBD, CBG, CBC, CBDA) often, but not always block growth of cancer cells in vitro and display a variety of anti-neoplastic effects in vivo, though typically at very high doses that would not be seen clinically.
- While limited evidence from one observational study suggests cancer patients use cannabis to alleviate symptoms associated with cancer (e.g. chemosensory alterations, weight loss, depression, pain), there has only been one limited clinical study in patients with glioblastoma multiforme, which reported that intra-tumoural injection of high doses of THC did not improve patient survival beyond that seen with conventional chemotherapeutic agents.

7.0 Adverse effects

7.1 Carcinogenesis and mutagenesis

- Evidence from pre-clinical studies suggests cannabis smoke contains many of the same carcinogens and mutagens as tobacco smoke and that cannabis smoke is as mutagenic and cytotoxic, if not more so, than tobacco smoke.
- However, limited and conflicting evidence from epidemiological studies has thus far been unable to find a robust and consistent association between cannabis use and various types of cancer, with the possible exception of a link between cannabis use and testicular cancer (i.e. testicular germ cell tumours).

7.2 Respiratory tract

- Evidence from pre-clinical studies suggests that cannabis smoke contains many of the same respiratory irritants and toxins as tobacco smoke, and even greater quantities of some such substances.

- Case studies suggest that cannabis smoking is associated with a variety of histopathological changes in respiratory tissues, a variety of respiratory symptoms similar to those seen in tobacco smokers, and changes in certain lung functions with frequent, long-term use.
- The association between chronic heavy cannabis smoking (without tobacco) and chronic obstructive pulmonary disease, is unclear, but if there is one, is possibly small.

7.3 Immune system

- Pre-clinical studies suggest certain cannabinoids have a variety of complex effects on immune system function (pro-/anti-inflammatory, stimulatory/inhibitory).
- The limited clinical and observational studies of the effects of cannabis on immune cell counts and effect on HIV viral load are mixed, as is the evidence around frequent cannabis use (i.e. daily/CUD) and adherence to ART.
- Limited but increasing evidence from case studies also suggests cannabis use is associated with allergic/hypersensitivity-type reactions.

7.4 Reproductive and endocrine systems

- Pre-clinical evidence suggests certain cannabinoids can have negative effects on a variety of measures of reproductive health. Furthermore, limited evidence from human observational studies with cannabis appears to support evidence from some pre-clinical studies.
- Evidence from human observational studies also suggests a dose- and age-dependent association between cannabis use and testicular germ cell tumours.
- Pre-clinical evidence clearly suggests in utero exposure to certain cannabinoids is associated with a number of short and long-term harms to the developing offspring.
- However, evidence from human observational studies is complex and suggests that while confounding factors may account for associations between heavy cannabis use during pregnancy and adverse neonatal or perinatal effects, heavy cannabis use during pregnancy is associated with reduced neonatal birth weight.

7.5 Cardiovascular system

- Pre-clinical studies suggest that ultra-low doses of THC may be cardioprotective on experimentally-induced myocardial infarction.
- Evidence from case and observational studies suggests that acute and chronic smoking of cannabis is associated with harmful effects on vascular, cardiovascular and cerebrovascular health (e.g. myocardial infarction, strokes, arteritis) especially in middle-aged (and older) users.
- However, a recent systematic review suggests that evidence examining the effects of cannabis on cardiovascular health is inconsistent and insufficient.

7.6 Gastrointestinal system and liver

- Evidence from case reports suggests chronic, heavy (THC-predominant) cannabis use is associated with an increased risk of cannabis hyperemesis syndrome (CHS).
- Limited evidence from observational studies suggests mixed findings between (THC-predominant) cannabis use and risk of liver fibrosis progression associated with hepatitis C infection.

7.7 Central nervous system

7.7.1 Cognition

- Evidence from clinical studies suggests acute (THC-predominant) cannabis use is associated with a number of acute cognitive effects.
- Evidence from observational studies suggests chronic cannabis use is associated with some cognitive and behavioural effects that may persist for varying lengths of time beyond the period of acute intoxication depending on a number of factors.
- Limited evidence from human clinical imaging studies suggests THC and CBD may exert opposing effects on neuropsychological/neurophysiological functioning.
- Evidence from mainly cross-sectional human clinical imaging studies suggests heavy, chronic cannabis use is associated with a number of structural changes in grey and white matter in different brain regions.
- Furthermore, early-onset use and use of high-potency, THC-predominant cannabis, has been associated with an increased risk of some brain structural changes and cognitive impairment.

7.7.2 Psychomotor performance and driving

- Evidence from experimental clinical studies suggests acute use of (THC-predominant) cannabis impairs a number of psychomotor and other cognitive skills needed to drive a motor vehicle.
- While chronic/frequent cannabis use may be associated with a degree of tolerance to some of the effects of cannabis in some individuals, chronic cannabis use can still pose risks to safe driving due, in part, to significant body burden of THC leading to a chronic level of psychomotor impairment.
- Evidence from clinical and epidemiological studies suggests a dose-response effect, with increasing doses of THC increasing the risk of motor vehicle crashes that can lead to injuries and death.
- Combining alcohol with cannabis (THC) is associated with an increased degree of impairment and increased risk of harm.

7.7.3 Psychiatric effects

7.7.3.1 Anxiety, PTSD, depression and bipolar disorder

- Evidence from clinical studies suggests a dose-dependent, bi-phasic effect of THC on anxiety and mood, where low doses of THC appear to have an anti-anxiety and mood-elevating effect whereas high doses of THC can produce anxiety and lower mood.
- Epidemiological studies suggest an association between (THC-predominant) cannabis use, especially chronic, heavy use and the onset of anxiety, depressive and bipolar disorders, and the persistence of symptoms related to PTSD, panic disorder, depressive disorder, and bipolar disorder.
- Preliminary evidence from surveys suggests an association between use of ultra-high-potency cannabis concentrate products (e.g. butane hash oil, BHO) and higher rates of self-reported anxiety and depression and other illicit drug use as well as higher levels of physical dependence than with high-potency herbal cannabis.

7.7.3.2 Schizophrenia and psychosis

- Evidence from clinical studies suggests that acute exposure to (THC-predominant) cannabis or THC is associated with dose-dependent, acute and transient behavioural and cognitive effects mimicking acute psychosis.
- Epidemiological studies suggest an association between (THC-predominant) cannabis use, especially early, chronic, and heavy use and psychosis and schizophrenia.
- The risk of schizophrenia associated with cannabis use is especially high in individuals who have a personal or family history of schizophrenia.
- Cannabis use is also associated with earlier onset of schizophrenia in vulnerable individuals and exacerbation of existing schizophrenic symptoms and worse clinical outcomes.

7.7.3.3 Suicidal ideation, attempts and mortality

- Evidence from epidemiological studies also suggests a dose-dependent association between cannabis use and suicidality, especially in men.

7.7.3.4 Amotivational syndrome

- The available limited evidence for an association between cannabis use and an “amotivational syndrome” is mixed.

Important Note: For the sake of completeness and for contextual purposes, the content in the following document includes information on dried cannabis and other cannabis-based products as well as selected cannabinoids. However, cannabis products and cannabinoids should not be considered equivalent even though the information on such products is presented together within the text. Cannabis and cannabis products are highly complex materials with hundreds of chemical constituents whereas cannabinoids are typically single molecules. Drawing direct comparisons between cannabis products and cannabinoids must necessarily take into account differences in the route of administration, dosage, individual pharmacological components and their potential interactions, and the different pharmacokinetic and pharmacodynamic properties of these different substances.

1.0 The Endocannabinoid System

The endocannabinoid system (ECS) **(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 ECS has been implicated in a very broad number of physiological as well as pathophysiological processes including nervous system 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/mood [2-4]. Furthermore, there is strong evidence that dysregulation of the ECS contributes to many human diseases including pain, inflammation, psychiatric disorders and neurodegenerative diseases [5].

Components of the endocannabinoid system

The ECS consists mainly of: the cannabinoid 1 and 2 (CB_1 and CB_2) receptors; the cannabinoid receptor ligands N-arachidonoylethanolamine ("anandamide") and 2-arachidonoylglycerol (2-AG); the endocannabinoid-synthesizing enzymes N-acyltransferase, phospholipase D, phospholipase C-β and diacylglycerol-lipase (DAGL); and the endocannabinoid-degrading enzymes fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL) **(Figure 1)** [2]. Anandamide and 2-AG are considered the primary endogenous activators 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, virodhamine, *N*-homo-γ-linolenoylethanolamine and *N*-docosatetraenoylethanolamine [2, 6-9]. Other 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) [9]. These fatty acyl ethanolamides 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 [10]. This type of effect has been generally referred to as the so-called "entourage effect" [10, 11]. The term "entourage effect" is also used in the context of the interactions between phytocannabinoids and terpenes in a physiological system (see **Section 1.1.2**).

Endocannabinoid synthesis

Endocannabinoids are arachidonic acid derivatives which are synthesized "on demand" (e.g. in response to an action potential in neurons or in response to another type of biological stimulus) from membrane phospholipid precursors in response to cellular requirements [2, 12-14]. Synthesis of endocannabinoids "on demand" ensures that endocannabinoid signaling is tightly controlled both spatially and temporally. Anandamide is principally, but not exclusively, produced by the transfer of arachidonic acid from phosphatidylcholine to phosphatidylethanolamine by N-acyltransferase to yield N-arachidonoylphosphatidylethanolamine (NAPE). NAPE is then hydrolyzed to form anandamide by a NAPE-specific phospholipase D [2, 15]. Other synthetic routes include acyl-chain removal from NAPE by α/β-hydrolase 4 to yield glycerophospho-N-arachidonoylethanolamine followed by phosphodiester bond hydrolysis of glycerophospho-N-arachidonoylethanolamine by phosphodiesterase 1 to yield anandamide [16]. 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 DAGL [2, 15]. While anandamide and 2-AG are both derivatives of arachidonic acid, they are synthesized by pathways distinct from those used to synthesize eicosanoids [17]. Nevertheless, it appears that there may be a certain amount of cross talk between the eicosanoid and endocannabinoid pathways [17].

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 (CBN) 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 [18, 19]. 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 [20]. The *CNR1* coding sequence consists of one exon encoding a protein of 472 amino acids [21]. The CB_1 receptor protein shares 97 – 99% amino acid sequence identity across species (human, rat, mouse) [21]. 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 [21]. 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 [21].

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, 13]. Anandamide is a partial agonist at cannabinoid receptors, and binds with slightly higher affinity at CB_1 compared to CB_2 receptors [2, 22]. 2-AG appears to bind equally well to both cannabinoid receptors (with slightly higher affinity to CB_1), but has greater potency and efficacy than anandamide at cannabinoid receptors [2, 22].

In the central nervous system (CNS), the overall effect of CB_1 receptor activation is suppression of neurotransmitter release (5-hydroxytryptamine (5-HT), glutamate, acetylcholine, GABA, noradrenaline, dopamine, D-aspartate, cholecystokinin) at both excitatory and inhibitory synapses with both short and long-term effects [2, 18, 23]. Inhibition of neurotransmitter release occurs through a retrograde signaling mechanism whereby endocannabinoids synthesized and released from the cell membrane of post-synaptic neurons diffuse backwards across the synaptic cleft and bind to CB_1 receptors located on the pre-synaptic terminals **(Figure 1)** [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 [19].

Cannabinoid receptor expression and receptor distribution

Most tissues contain a functional ECS 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 [19]. 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, the rostral ventrolateral medulla, the dorsal primary afferent spinal cord regions including peripheral nociceptors, and spinal interneurons [4, 23, 24]. CB_1 receptor density is highest in the cingulate gyrus, the frontal cortex, the hippocampus, the cerebellum, and the basal ganglia [5]. Moderate levels of CB_1 receptor expression are found in the basal forebrain, amygdala, nucleus accumbens, periaqueductal grey, and hypothalamus and much lower expression levels of the receptor are found in the midbrain, the pons, and the medulla/brainstem [5]. Relatively little CB_1 receptor expression is found in the thalamus and the primary motor cortex [5]. The CB_1 receptor is also expressed in many other organs and tissues including adipocytes, leukocytes, spleen, heart, lung, the gastrointestinal (GI) tract (liver, pancreas, stomach, and the small and large intestine), kidney, bladder, reproductive organs, skeletal muscle, bone, joints, and skin [25-43]. 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 [44, 45].

Other molecular targets for 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 (G protein-coupled receptor 55), the transient receptor potential (TRP) cation channel family, and a class of nuclear receptors/transcription factors known as the PPARs, as well as $5\text{-}HT_{1A}$ receptors, the α_2 adrenoceptors, adenosine and glycine receptors. For additional details on this subject please see **Section 2.1** and consult the following resources [8, 9, 22, 46-49]. 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: FAAH and MAGL [3]. FAAH is primarily localized post-synaptically [50, 51] and preferentially degrades anandamide [14]; MAGL is primarily localized pre-synaptically [50, 51] and favors the catabolism of 2-AG **(Figure 1)** [14]. Signal termination is important in ensuring that biological activities are properly regulated and prolonged signaling activity, such as by the use of cannabis, can have potentially deleterious effects [52, 53].

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

Dysregulation of the ECS appears to be connected to a number of pathological conditions, with the changes in the functioning of the system being either protective or harmful [54]. Modulation of the ECS either through the targeted inhibition of specific metabolic pathways, and/or directed agonism or antagonism of its receptors may hold therapeutic promise [13]. However, a major and consistent therapeutic challenge confronting the routine use of (THC-predominant) cannabis and psychoactive cannabinoids (e.g. THC) in the clinic has remained that of achieving selective targeting of the site of disease or symptoms and the sparing of other bodily regions such as the mood and cognitive centres of the brain [23, 54-57]. Despite this significant challenge, emerging evidence from clinical studies of smoked or vapourized (THC-predominant) cannabis for chronic non-cancer pain (mainly neuropathic pain) suggests that use of very low doses of THC (< 3 mg/dose) may confer therapeutic benefits with minimal psychoactive side effects [58, 59] (and also see **Section 3.0** and **4.7.2.2** for additional details).

Role of the endocannabinoid system in nervous system development

The CB_1 receptor is highly expressed in the developing brain [60]. For example, CB_1 receptors are highly expressed from early fetal stages, beginning as early as E12.5 (in mice) and into late fetal stages (E21) with high expression in white matter within a number of different structures including the hippocampus, cerebellum, caudate-putamen and cerebral cortex that continues to increase after birth and into adulthood; in contrast, after birth there is tapering of CB_1 receptor expression in other structures such as the corpus callosum, fornix, stria terminalis and the fasciculus retroflexus [60]. Furthermore, in the adult brain, the CB_1 receptor appears to be localized on the axonal plasma *membrane* and in somatodendritic endosomes, whereas in fetal brain the CB_1 receptor is mostly localized to endosomes both in axons and in the somatodendritic region [60]. The available evidence suggests a neurodevelopmental role for the ECS including in functions such as survival, proliferation, migration and differentiation of neuronal progenitors [60]. CB_1 receptor activation, in response to stimulation by endocannabinoids, such as 2-AG and anandamide, promotes these functions but delays the transition from multipotent, proliferating, and migration-competent progenitor phenotype towards a more settled, well-differentiated, post-mitotic neuronal phenotype [60, 61]. *In vitro* studies examining the effects of CB_1 receptor activation in primary neuronal cultures suggest that the CB_1 receptor is mainly a negative regulator of neurite growth since activation of the receptor results in growth cone arrest, repulsion or collapse and thereby influences the ability of axons to reach their targets [60]. However, these CB_1 receptor-mediated responses may be surmountable by the effects of local growth-promoting effectors at the growth cone and the balance between the effects of endocannabinoids and growth factors would determine the overall outcome of neuronal development. The CB_1 receptor appears also to act as a negative regulator of synaptogenesis and in doing so can also affect the fate of neuronal communication [60]. Exposure to cannabinoids that activate the CB_1 receptor (such as THC) during developmental periods of nervous system development such as during embryonic development in pregnancy could alter the course of normal neuronal development in offspring and negatively affect normal brain function potentially causing long-lasting impairment of a number of cognitive functions and behaviours [61] (and also see **Sections 2.5 and 7.4** for additional information). For example, a study conducted in pregnant mice using a low dose of THC has been shown to alter the expression level of 35 proteins in the fetal cerebrum [62]. Furthermore this study concretely identified a specific molecular target for THC in the developing CNS whose modifications can directly and permanently impair the wiring of neuronal networks during corticogenesis by enabling formation of ectopic neuronal filopodia and altering axonal morphology [62]. Another *in vitro* study with retinal ganglion cell explants showed that CBD decreased neuronal growth cone size and filopodia number as well as total projection length and induced growth cone collapse and neurite retraction (i.e. chemo-repulsion) through the GPR55 receptor [63].

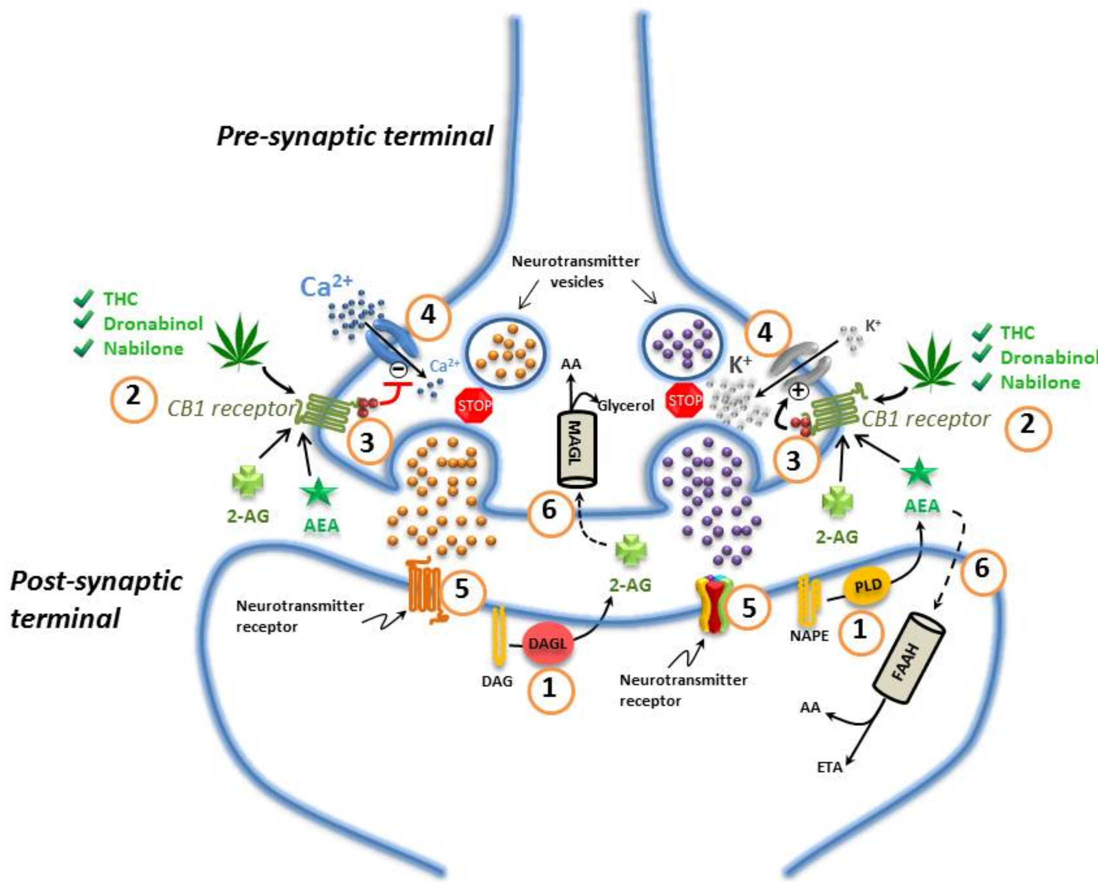


Figure 1. The Endocannabinoid System in the Nervous System

(1) Endocannabinoids are manufactured "on-demand" (e.g. in response to an action potential in neurons) 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 (anandamide (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 to and activate the pre-synaptic G-protein-coupled CB_1 receptors; **(3)** Binding of phytocannabinoid and endocannabinoid agonists to the CB_1 receptors triggers G_i/G_o protein signalling that, for example, inhibits adenylyl cyclase, thus decreasing the formation of cyclic AMP and the activity of protein kinase A; **(4)** Activation of the CB_1 receptor also results in G_i/G_o protein-dependent 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-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 (AA) and glycerol. See text for additional details. Figure adapted from [64-66].

1.1 Cannabis

1.1.1 Chemistry and composition

Cannabis sativa (i.e. cannabis, marihuana, marijuana) is a hemp plant that grows throughout temperate and tropical climates [67]. The leaves and flowering tops of *Cannabis* contain over 500 distinct compounds distributed among 18 different chemical classes, and harbor over 100 different phytocannabinoids [68-71] The principal phytocannabinoids appear to be delta-9-tetrahydrocannabinol (i.e. Δ^9-THC, THC), CBN, and cannabidiol (CBD) [72-74], although the relative abundance of these and other phytocannabinoids can vary depending on a number of factors such as the *Cannabis* strain, the soil and climate conditions, and the cultivation techniques [75, 76]. Other phytocannabinoids found in cannabis include cannabigerol (CBG), cannabichromene (CBC), tetrahydrocannabivarin (THCV) and many others [70]. In the living plant, these phytocannabinoids exist as both inactive monocarboxylic acids (e.g. tetrahydrocannabinolic acid, THCA) and as active decarboxylated forms (e.g. THC); however, heating (at temperatures above 120 °C) promotes decarboxylation (e.g. THCA to THC) [77-79]. Furthermore, pyrolysis (such as by smoking) 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, 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 [80]. Other phytocannabinoids (e.g. CBD, CBC, CBG) are present in lesser amounts in the plant and have little, if any, psychotropic properties [80]. However, Canadian licensed producers of cannabis for medical purposes have now made available a large variety of cannabis strains containing varying levels of THC and CBD, including THC-predominant, CBD-predominant or balanced strains for patients who have received authorization from their healthcare practitioner to access cannabis for medical purposes. For more information, please consult the Health Canada authorized licensed producers of cannabis for medical purposes website.

1.1.2 Other constituents

The large number of compounds found in cannabis spans many chemical classes including phytocannabinoids, 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 [70]. Furthermore, differences in the presence and the relative abundance of some of these various components have been investigated, and differences in various components have been noted between cannabis extract, vapour, and smoke, and also between cannabis varieties [81]. 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 [81-83]. Moreover, comparisons between cannabis smoke and tobacco smoke have shown that the former contains many of the same carcinogenic chemicals found in the latter [82, 84] (see **Section 7.1** for more information).

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 [75]. 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 [75], 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 [85, 86],i.e. the "entourage effect", 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 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 [87]. Complete decarboxylation of Δ^9-THCA to Δ^9-THC has been shown to occur starting at 98 °C and up to a temperature of 200 °C. As the temperature increases, the rate of decarboxylation increases: it takes 4 hours for complete decarboxylation at 98 °C, but only seconds at 200 °C [88-90]. Heat, light, humidity, acidity and oxidation all affect the stability of cannabis and phytocannabinoids [91, 92]. The National Institute on Drug Abuse reports that retention samples of their carefully prepared and standardized cigarettes are stable for months, particularly when stored below 0 ºC (-18 ºC) in the dark, in tightly-closed containers [93]. Even when stored at +18 ºC, only a third of the Δ^9-THC content is lost over a five-year period with some increase in the concentration of CBN. Cannabis cigarettes with lower Δ^9-THC content (1.15% THC) appear to lose more Δ^9-THC compared to cigarettes with higher Δ^9-THC content (2.87% THC) [93]. Turner et al. found that the THC content of cannabis decayed at a rate of 3.83, 5.38, and 6.92% per year for cannabis stored at -18 ºC, 4 ºC and 22 ºC respectively [94]. Sevigny has provided the following formula for calculating decay of THC: $THC_0 = THC_a / e^{-(k)(t)}$ where THC_0 is the unknown initial concentration of THC, THC_a is the assayed concentration of THC, k is the decay rate constant which can vary according to two conditions: $k = 0.0263$ (the lower-bound average decay rate for samples stored in darkness at 3 ºC) and $k = 0.0342$ (the upper-bound average decay rate for samples stored in natural light of a laboratory at 22 ºC), and t is the seizure-to-assay analysis lag (in months) [95]. For specific stability and storage conditions for cannabis provided by licensed commercial producers in Canada, please consult information provided by the licensed commercial producers.

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 [46, 48, 96], has activity at non-CB receptors and other targets [46, 48, 97], and is responsible for the psychoactive and potential therapeutic effects of cannabis through its actions at the CB_1 receptor [46, 48, 98]. Δ^8-THC (an isomer of Δ^9-THC) is found in smaller amounts in the plant, 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 [96]. An *in vivo* animal study and one clinical study suggest Δ^8-THC to be a more potent anti-emetic than Δ^9-THC [99, 100].

CBN is a product of Δ^9-THC oxidation and has 10% of the activity of Δ^9-THC at the CB_1 receptor [101]. Its effects are not well studied but it appears to have some possible immunosuppressive properties in a small number of *in vitro* studies [102].

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 [49, 101, 103, 104]. For example, *in vitro* assays have shown that CBG, at a concentration of 100 µg/ml (approximately equivalent to a concentration of 300 µM and above the typical physiological range, and therefore not truly representative of human *in vivo* conditions), is associated with a greater than 30% inhibition of cyclooxygenase (COX) 1 and 2 enzymes, but only produced weak inhibition (<10%) of prostaglandin production *in vivo* at concentrations that did not cause cytotoxicity [104]. Cannabigerolic acid has a similar profile. CBG has also been shown to block $5\text{-}HT_{1A}$ receptors and act as an α_2-adrenoceptor agonist [105]. There is some emerging evidence that suggests CBG can produce signs of analgesia by activation of α_2-adrenoceptors [46].

CBD lacks detectable psychoactivity and does not appear to bind to either CB_1 or CB_2 receptors at physiologically meaningful concentrations, but there is some emerging evidence suggesting it may act as a non-competitive, negative, allosteric modulator of CB_1 receptors [106]. There is also a considerable body of evidence suggesting CBD also affects the activity of a significant number of other targets including ion channels, receptors, and enzymes [18, 101, 107]. For example, CBD has been shown to block the activity of FAAH resulting in an increase in anandamide levels, act as an agonist of the TRPV1 channel, inhibit adenosine uptake by acting as an indirect agonist at adenosine receptors, act as an agonist of $5\text{-}HT_{1A}$ receptors, act as a positive allosteric modulator of glycine receptors, and act as an anti-oxidant and reactive oxygen species scavenger as well as regulating calcium homeostasis via the mitochondrial sodium/calcium (Na^+/Ca^{2+})-exchanger [108]. The effects of CBD at these and other molecular targets are associated with anti-inflammatory, analgesic, anti-nausea, anti-emetic, anti-psychotic, anti-ischemic, anxiolytic, and anti-epileptiform effects [101, 108, 109].

THCV acts as a CB_1 receptor antagonist and CB_2 receptor partial agonist *in vitro* and *in vivo* [110, 111], as well as a $5\text{-}HT_{1A}$ receptor agonist [47] and pre-clinical studies suggest it may have anti-epileptiform/anti-convulsant, anti-nociceptive and potential anti-psychotic properties [47, 108, 112].

Much of what is known about the beneficial properties of the non-psychotropic cannabinoids (e.g. CBD, THCV) is derived from *in vitro* and *in vivo* studies and few well-conducted, rigorous clinical studies of these substances exist. However, the results from these pre-clinical 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 [18, 101, 113]. For more in-depth information on the pharmacology of cannabinoids, the reader is invited to consult the following resources [22, 46, 48, 101, 114].

Phytocannabinoid-phytocannabinoid interactions and phytocannabinoid differences among cannabis strains

Despite anecdotal claims, there is limited reliable information regarding actual 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 [46, 48, 106, 115-136]. 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 with Δ^9-THC), 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 [123].

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 [123, 129], and those of a *pharmacodynamic* origin [133, 135]. 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). Potentiation of THC effects by CBD may be caused by inhibition of THC metabolism in the liver, resulting in higher plasma levels of THC [123, 129]. *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 [120, 134], whereas CBD appears to potentiate some of the effects associated with THC when the CBD to THC ratio is around 2 : 1 [120]. Some emerging *pre-clinical* evidence suggests combined anti-emetic sub-threshold doses of THC and CBD or cannabidiolic acid (CBDA) may be effective in animal models of acute nausea and/or anticipatory nausea (see **Section 4.3** for additional details).

Psychological and physiological effects associated with varying phytocannabinoid concentrations

A number of studies have examined the neurophysiological, cognitive, subjective, or behavioural effects of varying the concentrations of Δ^9-THC, CBD, or other cannabinoids such as CBC in smoked cannabis [128, 137]. 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 [128]. 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 [137]. This double-blind, placebo-controlled, within-subject, crossover clinical study reported few reliable differences between the THC-only and whole-plant cannabis conditions [137]. 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 [138], (see **Section 4.7.2.3**. 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 [122]. 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" [122].

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 symptoms (an effect typically associated with exposure to higher doses of THC) [139]. 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.

Brunt et al. (2014) conducted a study examining the self-reported therapeutic satisfaction and subjective effects of different strains of pharmaceutical-grade cannabis sold in the Netherlands [118]. The authors reported that among the study population of about 100 patients using medical cannabis for conditions such as multiple sclerosis (MS), chronic pain, nausea, cancer and psychological problems, those who used cannabis with cannabinoid concentrations of 6% THC and 7.5% CBD (i.e. "low THC" cannabis) reported significantly less anxiety and dejection (i.e. feeling down, sad, depressed), but also reported less appetite stimulation. Importantly, those patients using the "low THC" condition reported equivalent levels of therapeutic satisfaction as those patients who reported using "high THC" (19% THC, < 1% CBD) and "medium THC" (12% THC, < 1% CBD) cannabis. There was also surprisingly little difference in terms of daily gram amount used between the different THC/CBD varieties with all categories reporting, on average, use of less than one gram of dried cannabis per day. The study findings are also consistent with the rest of the literature in terms of the average daily gram dose of dried cannabis used by patients (i.e. up to 3 g at most, but generally around one gram or less of variable THC content). Taken together, the study suggests that the use of cannabis containing approximately equivalent "lower" levels of THC and "higher" levels of CBD is associated with self-reported therapeutic efficacy and satisfaction across a number of different medical conditions for which dried cannabis is typically used, and also associated with attenuated levels of mood perturbation. The evidence also suggests that cannabis containing higher levels of THC and little CBD is not necessarily more effective than lower dose strains, except for stimulation of appetite.

However, the study findings suggest that the use of higher-THC strains is associated with greater mood perturbation than the lower-THC strains. The study carried a number of caveats being that it only looked at a small number of patients, had a limited number of medical conditions and consisted of a self-reported survey.

Two *in vivo* studies conducted in non-human primates (i.e. rhesus monkeys) showed that CBD attenuated some of the effects of THC including cognitive-impairing effects and disruption of motor inhibitory behaviour [115, 119].

An *in vivo* study conducted in non-human primates (i.e. rhesus monkeys) showed that CBD, administered in a 1 : 1 ratio with THC, attenuated some of the cognitive-impairing effects of THC, especially effects on spatial memory, but not on THC-induced performance deficits (i.e. non-specific motor and motivational effects) [119]. Another *in vivo* study conducted in non-human primates (i.e. rhesus monkeys) examining the acute and chronic effects of CBD on THC-induced disruption of motor inhibitory behaviour showed that CBD, at ratios of 3 : 1 but not 1 : 1 relative to THC, attenuated some of the acute and chronic behavioural effects of higher-dose THC on disruption of motor inhibitory behaviour [115].

In summary, although it appears that CBD may modulate some of the behavioural effects of THC, 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.

Overview of pharmacological actions of cannabis

Most of the available information regarding the acute and long-term effects of cannabis use comes from studies conducted on non-medical 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 marijuana "high") as well as cardiovascular, bronchopulmonary, ocular, psychological and psychomotor effects. Euphoria typically occurs shortly after smoking and generally takes longer with oral administration [80]. However, some people can experience dysphoria and anxiety [140]. Tachycardia is the most consistent of the acute physiological effects associated with the consumption of cannabis [141-144].

The short-term psychoactive effects associated with cannabis smoking in non-medical 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 [145]. This is followed by a depressant period [146]. Most reviews note that cannabis use is associated with impaired function in a variety of cognitive and short-term memory tasks [102, 146-151] and the levels of Δ^9-THC in the plasma after smoking appear to have a dose, time, and concentration-dependent effect on cognitive function [152-154]. Driving and operation of intricate machinery, including aircraft, may be significantly impaired [155-158].

Table 1 (below), adapted from a review [159], 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 [141, 160, 161]. Effects differ greatly among individuals and may be greater in those who are young, severely ill, elderly, or in those taking other drugs.

Table 1: Selected Pharmacologic Actions of Cannabis/Psychoactive Cannabinoids (mainly in reference to THC-predominant cannabis) (**selected, non-exhaustive list of sources*)
For additional information please see the text.

Body System/Effect	Detail of Effects
Central Nervous System (CNS)	
Psychological (**Sections 4.9.5** and **7.7**)	Euphoria ("high"), dysphoria, anxiety, depersonalization, precipitation or aggravation of psychosis, schizophrenia or bipolar disorder (esp. in vulnerable individuals) and suicidal ideation/attempts (esp. among men), limited and mixed evidence in PTSD, mixed evidence for amotivational syndrome [80, 162-203].
Perception (**Section 7.7.1**)	Heightened sensory perception, distortion of space and time sense, hallucinations, misperceptions [175, 179, 190, 204-211].
Sedative (**Sections 6.2** and **7.7**)	Generalized CNS depression, drowsiness, somnolence (dose-dependent effect on sleep); additive with other CNS depressants (opioids/alcohol) [59, 141, 162, 172, 176, 179, 184, 185, 195, 212-227].
Cognition, psychomotor performance (**Sections 7.7.1** and **7.7.2**)	Fragmentation of thoughts, mental clouding (attention and concentration), memory impairment/amnesia, global impairment of performance especially in complex and demanding tasks and additive effect with other CNS depressants (e.g. alcohol) [128, 149-151, 155-158, 185, 205, 206, 227-235].
Motor function (**Sections 4.9.1** and **7.7.2**)	Incoordination, ataxia, falls, dysarthria, weakness [141, 172, 174, 176, 180, 206, 207, 222, 227, 236-240]. Limited and mixed evidence in dystonia, Huntington's disease, Tourette's syndrome and Parkinson's disease [179, 241-261].
Epilepsy (**Section 4.6**)	Anti-epileptiform and anti-convulsive properties with CBD (and possibly also with CBDV and THCV) [215, 217, 262-264]. Mixed pro- and anti-epileptiform and pro- and anti-convulsive effects with THC [263, 265, 266].
Analgesic (**Section 4.7**)	Limited evidence of mixed effects for acute pain [267-274]. Modest effect for chronic non-cancer pain (mainly neuropathic) [58, 59, 108, 176, 179, 184, 185, 195, 218, 222, 225, 226, 268, 273, 275-281] Modest/mixed effect for cancer pain [138, 282-285]. Mixed "opioid-sparing" effect [138, 280, 284, 286-288]. Very limited evidence for mixed effects for headache and migraine [289-293].
Anti-nausea/anti-emetic; hyper-emetic (**Sections 4.3** and **7.6.1**)	Observed with acute doses [109, 286, 294-297]. Tolerance may occur with chronic use [298]. Conversely, nausea and/or vomiting may also be observed with use for medical purposes [227]. Hyperemesis has also been observed with larger doses or chronic use in non-medical contexts [299-309].
Appetite (**Sections 4.4** and **4.9.8.4**)	Increased in normal, healthy subjects, but also in patients suffering from HIV/AIDS-associated anorexia/cachexia [118, 179, 223, 224, 227, 310-313]. Evidence mixed and modest for loss of appetite in cancer [314-321]. Evidence weak for anorexia nervosa [322, 323].
Tolerance (**Section 2.4**)	To most behavioural and somatic effects, including the "high" (with chronic use) [181, 229, 324-333].
Dependence, withdrawal syndrome (**Section 2.4**)	Dependence has been produced experimentally, and observed clinically, following prolonged intoxication [145, 162, 190, 329, 334-337]. Abstinence leads to withdrawal symptoms which can include anger, anxiety, restlessness, irritability, depressed mood, disturbed sleep, strange dreams, decreased appetite, and weight loss [190, 329, 338-342].
Cardiovascular and Cerebrovascular System	
Heart rate/rhythm (**Section 7.5**)	Tachycardia with acute dosing; tolerance developing with chronic exposure [141-144, 184, 185, 343-346]. Premature ventricular contractions, palpitations, atrial fibrillation, ventricular arrhythmia also seen with acute doses [144, 227, 347-351].
Peripheral circulation (**Section 7.5**)	Vasodilatation, conjunctival redness, supine hypertension, postural hypotension [219, 227, 345, 347, 352-354].
Cardiac output (**Section 7.5**)	Increased cardiac output [347] and myocardial oxygen demand [352].
Cerebral blood flow (**Section 7.5**)	Increased with acute dose, decreased with chronic use, region-dependent variations [345, 355].
Myocardial infarction (**Section 7.5**)	Increased risk of acute myocardial infarction within one hour after smoking cannabis especially in individuals with existing cardiovascular disease [144, 352].
Stroke (**Section 7.5**)	Increased risk of experiencing stroke after an acute episode of smoking cannabis [347, 356, 357].

Body System/Effect	Detail of Effects
Carcinogenesis/mutagenesis	
(**Section 7.1**)	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 [82, 84]. Conflicting evidence linking cannabis smoking and cancer [358-361]. Possible link between cannabis smoking and testicular cancer [362].
Respiratory System	
Histopathological changes/ inflammation (**Section 7.2**)	Chronic cannabis smoking associated with histopathological changes in the lung (basal cell hyperplasia, stratification, goblet cell hyperplasia, cell disorganization, inflammation, basement membrane thickening, and squamous cell metaplasia) [363]. Long-term smoking associated with cough, increased production of phlegm, and wheeze [364].
Bronchodilatation (**Sections 4.9.3** and **7.2**)	Acute THC exposure causes dilatation; possibly reversed with chronic exposure (by smoking) [364]. Smoked/vapourized cannabis may worsen asthmatic symptoms [365, 366].
Pulmonary function (FEV_1; FVC) (**Section 7.2**)	Acute, low-level exposure possibly stimulatory; long-term, heavy smoking possibly associated with decreased lung function [364, 367-371].
Gastrointestinal System	
(**Sections 4.9.8** and **7.6**)	Decreased gastrointestinal motility, decreased secretion, decreased gastric/colonic emptying, anti-inflammatory actions, limited and mixed evidence of benefit in irritable bowel syndrome and inflammatory bowel disease [33, 185, 279, 372]. Abdominal pain, nausea, vomiting, diarrhea [227].
Liver (**Sections 4.9.8.3** and **7.6.2**)	Increased risk of hepatic steatosis/fibrosis, especially in patients with Hepatitis C [35, 373-375]. Increased Hepatitis C treatment adherence resulting in a potential sustained absence of detectable levels of Hepatitis C virus [376].
Pancreas (**Section 4.9.8.5**)	Risk of acute pancreatitis with chronic, daily, heavy use [377-381].
Musculoskeletal system	
(**Sections 4.5.1**, **4.5.3** and **4.8**)	Possible positive effect in chronic pain associated with rheumatoid arthritis [382-384] and fibromyalgia [184, 385, 386]. May attenuate spasticity from MS and spinal cord injury [225, 226, 278, 387]. May negatively affect bone healing [388].
Eye	
(**Section 4.9.2**)	Limited evidence for decreased intraocular pressure [389-391].
Immune System	
(**Section 7.3**)	Complex immunomodulatory effects with suppressive and/or stimulatory effects (acute and chronic dosing) [26, 392]. Hypersensitivity/allergic reactions [365, 366, 393, 394].
Reproductive System	
Males (**Sections 2.5** and **7.4**)	Follicle stimulating hormone (FSH), luteinizing hormone (LH) and testosterone levels either unaffected or decreased with chronic cannabis smoking [395] (but see [396] which reports increased testosterone levels). Decreased sperm concentration and sperm count and altered morphology with chronic cannabis smoking in men [395, 396]. Decreased sperm motility, capacitation and acrosome reaction with *in vitro* THC exposure [395]. Dose-dependent stimulatory (low-dose) or inhibitory (high-dose) effects on sexual behaviour in men [395, 397] (but see [398] which suggests increased coital frequency with increased frequency of use in men and women).
Females (**Sections 2.5** and **7.4**)	Acute administration of THC suppresses release of gonadotropin-releasing hormone (GnRH) and thyrotropin-releasing hormone (TRH) with decreased release of prolactin and gonadotropins (FSH and LH) in animal and human studies [399]. Association between cannabis use and menstrual cycle disruptions in women including: slightly elevated rate of menstrual cycles lacking ovulation (i.e. anovulatory cycles), higher risk of decreased fertility, prolonged follicular phase/delayed ovulation, though evidence is mixed [399]. Chronic/sub-chronic administration of THC in animals: altered hypothalamic-pituitary-ovarian (HPO) axis function, disruption of follicular development, decreased estrogen and progesterone production, blocking of LH surge, anovulation [399]. Cannabis can alter HPO axis functionality and ovarian hormones produced by the HPO axis [399]. Dose-dependent

Body System/Effect	Detail of Effects
	stimulatory (low-dose) or inhibitory (high-dose) effects on sexual behaviour in women [397] (but see [398] which suggests increased coital frequency with increased frequency of use in men and women).

2.2 Pharmacokinetics

This section covers 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). See **Figure 2** (below) for a graphical representation of the pharmacokinetics of THC.

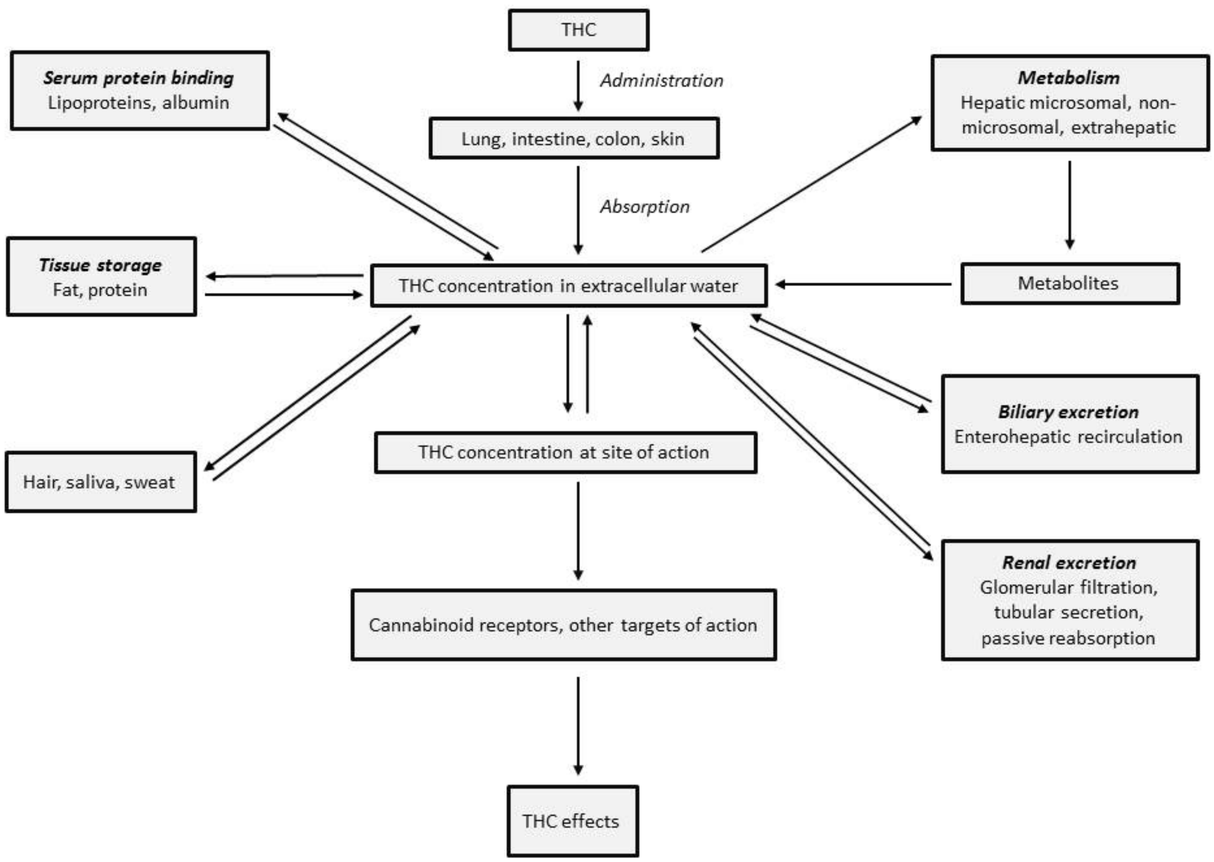


Figure 2. Pharmacokinetics of THC (and other cannabinoids). Figure adapted from [400].
THC (and other cannabinoids) can be administered by inhalation (e.g. smoking/vapourizing), orally (e.g. edibles, capsules, sprays), rectally (e.g. suppositories) or dermally (e.g. topicals) resulting in absorption through the lung, intestine, colon or skin. The concentration of THC (and other cannabinoids) in the extracellular water varies depending on serum protein binding (lipoproteins, albumin), tissue storage (fat, protein), metabolism (hepatic microsomal, non-microsomal, extrahepatic), biliary excretion (enterohepatic recirculation) and renal excretion (glomerular filtration, tubular secretion, passive reabsorption). The metabolism of THC (and other cannabinoids) produces metabolites which can also be found in the extracellular water. The concentration of THC in the extracellular water affects the THC (and other cannabinoids) concentration at the site of action. The effects of THC (and other cannabinoids) are observed when THC (and other cannabinoids) interacts with cannabinoid receptors or other targets of action. THC (and other cannabinoids) can also be detected in hair, saliva and sweat.

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 *acute* pharmacodynamic effects compared to oral administration [78]. The amount of Δ^9-THC (and other cannabinoids) delivered from cannabis cigarettes is not uniform and is a major variable in the assessment of absorption [78]. Uncontrolled factors include the source of the plant material and the composition of the cigarette/joint, together with the efficiency and method of smoking used by the subject [78, 401]. While it has been reported that smokers can titrate their Δ^9-THC intake, to a certain extent, by adapting their smoking behaviour to obtain desired levels of Δ^9-THC [402], other reasons may also explain the observed variation in smoking topography [403]. As mentioned, Δ^9-THC absorption by inhalation is extremely rapid but quite variable, with a bioavailability of 2 to 56% through the smoking route depending on depth of inhalation, puff duration, and breathhold [400, 404]. In practice, a maximum of 25 to 27% of the THC content in a cannabis cigarette is absorbed or delivered to the systemic circulation from the total available amount [141, 405]. It has been estimated that between 2 and 44 µg of THC penetrates the brain following smoking of a cannabis cigarette containing 2 to 22 mg of THC (e.g. 1 g joint containing 0.2 – 2.2% THC, delivering between 0.2 and 5.5 mg of THC based on a smoked bioavailability of 10 to 25%) [406].

The relationships between cannabis Δ^9-THC content, dose administered, and resultant plasma levels have been investigated. Mean plasma Δ^9-THC concentrations were 7.0 ng/mL and 18.1 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) [78]. 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 [407]. 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 [408]. Smoking a 25 mg dose of cannabis in a pipe 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 [59]. Smoking one cannabis cigarette (800 mg) containing 6.8% THC, (w/w) yielding a total THC content of 54 mg per cigarette was associated with a median whole blood peak THC concentration of approximately 60 ng/mL Δ^9-THC (occurring 15 min after starting smoking) [409]. Compared to the data available for absorption with smoked THC, there is far less such information available for smoked CBD. In one early clinical study, smoking one cannabis cigarette containing 19 mg CBD (~2.4% CBD) was associated with a mean peak blood plasma level of CBD of 110 ng/mL (range: 42 – 191 ng/mL) at 3 min post-dose [410]. The estimated systemic bioavailability of CBD by smoking was 31 % (range: 11 – 45%), generally similar to that seen with Δ^9-THC.

2.2.1.1 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, and tar, as well as a more efficient extraction of Δ^9-THC (and CBD) from the cannabis material [402, 411-414]. The subjective effects and plasma concentrations of Δ^9-THC obtained by vapourization of cannabis are comparable to those obtained by smoking cannabis [402]. In addition, the study reported that vapourization was well tolerated with no reported adverse effects, and was preferred over smoking by the test subjects [402]. While vapourization has been reported to be amenable to self-titration (as has been claimed for smoking) [402, 413], the proper use of the vapourizer for optimal administration of cannabis for therapeutic purposes needs to be established in more detail [414]. The amount and type of cannabis placed in the vapourizer, the vapourizing temperature and duration of vapourization, and, in the case of balloon-type vapourizers, the balloon volume are some of the parameters that can affect the delivery of Δ^9-THC and other phytocannabinoids [413]. Bioequivalence of vapourization compared to smoking has not been thoroughly established. Inhalation of vapourized cannabis (900 mg 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 [280]. Peak Δ^9-THC concentration (C_{max}) was achieved at 3 min in all study participants [280]. No statistically significant changes were reported for the AUC_{12} (12-hour area-under-the-curve) for either morphine or oxycodone, but there appeared to be a statistically significant decrease in the C_{max} of morphine sulfate, and a delay in the time needed to reach C_{max} for morphine during cannabis exposure [280]. One clinical study reported that vapourizing 500 mg cannabis containing low-dose (2.9%) THC (~14.5 mg THC), or high-dose (6.7%) THC (~33.5 mg THC) was associated with median whole-blood C_{max} values of 32.7 (low-dose) and 42.2 ng/mL (high-dose) THC, and median plasma C_{max} values of 46.5 (low-dose) and 62.1 ng/mL (high-dose) THC at 10 min post-inhalation respectively [206]. Median whole-blood C_{max} values for 11-hydroxy-THC were 2.8 (low-dose) and 5.0 ng/mL (high-dose) and median plasma C_{max} values were 4.1 (low-dose) and 7 ng/mL (high-dose) at 10 – 11 min post-inhalation respectively. Another clinical study reported that vapourizing cannabis with 11 – 12% THC content (administered dose of 300 µg/kg) was associated with mean plasma concentrations of 73.8 ng/mL THC and 6.9 ng/mL 11-hydroxy-THC 5 min post-vapourization [415]. A different clinical study showed that inhalation of 8 to 12 puffs of vapourized cannabis containing either 2.9% or 6.7% THC (400 mg each) was associated with a blood plasma C_{max} of 68.5 ng/mL and 177.3 ng/mL respectively and median blood plasma concentration of 23 and 47 ng/mL respectively [416]. Plasma C_{max} of 11-hydroxy-THC was 5.6 and 12.8 ng/mL for the 2.9 and 6.7% doses, respectively.

2.2.1.2 Oral

Whereas the acute effects on the CNS and physiological effects occur within minutes by the smoking route or by vapourization [149, 417], the acute effects proceed on a time scale of hours in the case of oral ingestion [417, 418]. Acute 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 [78]. 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 among non-medical users [419].

For orally administered prescription cannabinoid medicines such as synthetic Δ^9-THC (dronabinol, formerly marketed as Marinol®), only 10 to 20% of the administered dose enters the systemic circulation indicating extensive hepatic first-pass metabolism [227]. 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) [227]. 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) [227]. Again, the mean time to peak plasma Δ^9-THC concentration ranged from 30 min to 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 [227]. 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 [420].

A phase I study evaluating the pharmacokinetics of three oral doses of THC (3 mg, 5 mg and 6.5 mg) in 12 healthy older subjects (mean age 72, range: 65 – 80 years) showed wide inter-individual variation in plasma concentrations of THC and 11-hydroxy-THC[180]. For those subjects who reached C_{max} within 2 hours, the mean THC concentration was 1.42 ng/mL (range: 0.53 – 3.48 ng/mL) for the 3 mg dose, 3.15 ng/mL (range: 1.54 – 6.95 ng/mL) for the 5 mg dose, and 4.57 ng/mL (range: 2.11 – 8.65 ng/mL) for the 6.5 mg dose.

A randomized, double-blind, placebo-controlled, cross-over trial that evaluated the pharmacokinetics of oral THC in 10 older patients with dementia (mean age 77 years) over a 12-week period reported that median time to reach C_{max} (T_{max}) was between one and two hours with THC pharmacokinetics increasing linearly with increasing dose, but again with wide inter-individual variation [421]. Patients received 0.75 mg THC orally twice daily over the first six weeks and 1.5 mg THC twice daily over the second six-week period. The mean C_{max} after the first 0.75 mg THC dose was 0.41 ng/mL and after the first 1.5 mg THC dose was 1.01 ng/mL. After the second dose of 0.75 mg THC or 1.5 mg THC, the C_{max} was 0.50 and 0.98 ng/mL respectively.

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 [401], with a systemic availability of only 4 to 12% [407]. While most subjects displayed peak plasma Δ^9-THC concentrations (6 ng/mL) between one and two hours after ingestion, some of the 11 subjects in the study only peaked at 6 h, and many had more than one peak [78]. 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 [418]. Peak effects occurred 2.5 to 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 [137]. Ingestion of brownies containing a higher 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 depending on whether the THC in the brownie came from plant material or was added as pure THC [137]. 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 [137]. Tea made from dried cannabis flowering tops (19.1% Δ^9-THCA, 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 extensive hepatic first-pass effect [422].

After oral administration of chocolate cookies containing 40 mg CBD in healthy human subjects, mean plasma CBD levels ranged between 1.1 and 11 ng/mL (mean: 5.5 ng/mL) after one hour and the course of CBD in the plasma over six hours was in the same range as the course after 20 mg THC [423]. Daily oral doses of 10 mg/kg CBD for six weeks resulted in a mean weekly plasma concentration of 5.9 – 11.2 ng/mL [424]. Oral intake of 5.4 mg CBD resulted in plasma CBD concentrations ranging between 0.2 and 2.6 ng/mL (mean: 0.95 ng/mL) after one hour [425]. Bioavailability through the oral route was estimated at 6% [423, 426].

While cannabinoids are lipophilic and anecdotal evidence suggests that cannabinoids dissolve better in fats and oils, the influence of various fats on cannabinoid absorption *in vivo* has been poorly studied. A pre-clinical study examined the effect of dietary fats on THC and CBD absorption in in rats [427]. A dose of 12 mg/kg of THC or CBD in either lipid-free formulation or lipid long-chain triglycerides (LCT)-based formulation (sesame oil) was administered to rats by oral gavage. The absolute bioavailability of THC was 2.5 times higher in the lipid-based (C_{max} = 172 ng/mL; AUC = 1050 h.ng/mL) versus lipid-free formulation (C_{max} = 65 ng/mL; AUC = 414 h.ng/mL). The absolute bioavailability of CBD was three times higher in the lipid-based (C_{max} = 308 ng/mL; AUC = 932 h.ng/mL) versus lipid-free formulation (C_{max} = 87 ng/mL; AUC = 327 h.ng/mL). Furthermore, an *in vitro* lipolysis model was used to assess the mechanism by which lipids could enhance the bioavailability of THC and CBD. Results showed that 30% of THC and CBD was solubilized in the micellar layer and therefore was readily available. Incubation studies suggested that cannabinoids have a 70 to 80% association range with natural chylomicrons from rat and human. Chylomicrons act as carriers in the intestine and potentially transfer THC and CBD to the systemic circulation via the intestinal lymphatic system and therefore avoid hepatic first-pass metabolism, which would explain the increased bioavailability with the lipid-based formulation. The authors concluded that administration of cannabinoids with a fatty meal or in the form of a lipid-rich cannabis-containing cookie may increase systemic exposure and therefore change the efficacy of the drug by turning a barely effective dose into a highly effective one, or even, a therapeutic dose into a toxic one.

In vitro and *in vivo* studies suggest that exposure of CBD to (simulated) gastric fluid results in the conversion of CBD to THC and hexahydrocannabinols [428, 429]. In mice, it was shown that hexahydrocannabinols could, as is typically observed with THC, produce cataleptogenic effects [429]. The clinical implications of this conversion of CBD to THC and hexahydrocannabinols are the subject of heated debate and currently unclear.

Comparing smoked, vapourized and oral administration

A randomized, double-blind, placebo-controlled, double-dummy, cross-over clinical study examined the pharmacokinetics of THC and its phase I and II metabolites between frequent and occasional cannabis smokers after smoked, vapourized and oral cannabis administration [430]. Cannabis plant material (800 mg) containing 6.9% THC and 0.20% CBD was used, delivering a maximal THC dose of 51 mg and a maximal CBD dose of 1.5 mg. Vapourization was carried out using the Volcano® vapourizer (210 °C). Cannabis was administered orally by ingestion of cannabis-containing brownies. In *frequent* cannabis smokers (≥ five times per week over previous three months), the mean baseline-adjusted THC C_{max} after smoking was 151 ng/mL, after vapourization it was 85 ng/mL, and after oral consumption it was 15 ng/mL. Mean T_{max} was 7 min (smoking), 5 min (vapourization), and 2.5 h (oral). The mean $AUC_{0–72\ h}$ (ug · h/L) was 200 (smoking), 174 (vapourization), and 167 (oral). In *occasional* cannabis smokers (> two times per month but ≤ three times per week), the mean baseline-adjusted THC C_{max} after smoking was 52 ng/mL, after vapourization it was 48 ng/mL, and after oral consumption it was 10 ng/mL. Mean T_{max} was 7 min (smoking), 7 min (vapourization), and 2.3 h (oral). The mean $AUC_{0–72\ h}$ (ug · h/L) was 20 (smoking), 12 (vapourization), and 43 (oral). In *frequent* cannabis smokers, the mean baseline-adjusted 11-hydroxy-THC C_{max} after smoking was 9 ng/mL, after vapourization it was 5 ng/mL, and after oral consumption it was 7 ng/mL. Mean T_{max} was 13 min (smoking), 11 min (vapourization), and 2.3 h (oral). The mean $AUC_{0–72\ h}$ (ug · h/L) was 31 (smoking), 27 (vapourization), and 52 (oral). In *occasional* cannabis smokers, mean baseline-adjusted C_{max} after smoking was 3 ng/mL, after vapourization it was 2 ng/mL, and after oral consumption, it was 5 ng/mL. Mean T_{max} was 13 min (smoking), 6 min (vapourization), and 2.4 h (oral). The mean $AUC_{0–72\ h}$ (ug · h/L) was 3 (smoking), 2 (vapourization), and 33 (oral). These findings suggest, among other things, that peak blood THC concentration (THC C_{max}) was significantly lower after oral consumption compared to either route of inhalation and time to peak blood THC concentration (T_{max}) occurred significantly later for oral consumption compared to inhalation for both frequent and occasional cannabis smokers. In addition, C_{max} was significantly higher for the smoking route compared to vapourization, but only among frequent cannabis smokers. In addition, THC C_{max} values were significantly greater among frequent smokers compared to occasional smokers after smoking and vapourization only, and 11-hydroxy-THC C_{max} values were significantly greater among frequent smokers regardless of route of administration.

2.2.1.3 Oro-mucosal and intranasal

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 to 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 [431]. 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 are comparable to those seen with oral administration of dronabinol [121, 431]. Oro-mucosal administration of nabiximols is also amenable to self-titration [122, 383, 432, 433].

A small number of pre-clinical studies have explored intranasal administration of both THC and CBD. In one study in rabbits, intranasal administration of a 1 mg/kg dose of THC in a liquid solution or in a chitosan-based gel formulation produced a C_{max} of 20 ng/mL and 31 ng/mL, with T_{max} of 20 and 45 min respectively, compared to intravenous administration where the C_{max} and T_{max} were 1475 ng/mL and 0 min respectively [434]. In rats, intranasal administration of 200 µg/kg CBD in various formulations yielded C_{max} values ranging from 20 – 35 ng/mL with T_{max} values ranging between 20 and 30 min; by comparison, intravenous administration yielded a C_{max} of 3 596 ng/mL [435].

2.2.1.4 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 [436-440]. Plasma concentrations of Δ^9-THC are dose and vehicle-dependent, and also vary according to the chemical structure of the THC ester [439]. In humans, rectal doses of 2.5 to 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 to 8 h, and peak plasma levels of carboxy-Δ^9-THC ranging between 6.1 and 42.0 ng/mL within 1 to 8 h after administration [436].

2.2.1.5 Topical

Cannabinoids are highly hydrophobic, making transport across the aqueous layer of the skin the rate-limiting step in the diffusion process [78]. No clinical studies have been published regarding the percutaneous absorption of cannabis-containing ointments, creams, or lotions. However, some pre-clinical research has been carried out on transdermal delivery of synthetic and natural cannabinoids using a dermal patch [441, 442]. 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 [441]. Permeation of CBD and CBN was found to be 10-fold higher than for Δ^8-THC [443]. Transdermal application of a gel containing CBD with or without permeation enhancers in hairless guinea pigs showed that C_{max} without the enhancer was 9 ng/mL, and 36 ng/mL with the enhancer, and that maximal concentrations (T_{max}) were reached by 38 and 31 h post-application, respectively [435]. Furthermore, steady-state concentrations were 6 and 24 ng/mL without and with the permeation enhancer, respectively. Another pre-clinical study of a transdermal CBD gel formulation (1% or 10%) applied with increasing daily dose of 0.6, 3.1, 6.2 and 62 mg/day yielded plasma concentrations of 4 ng/mL, 18 ng/mL, 33 ng/mL, and 1 630 ng/mL respectively [444]. Lastly, a pre-clinical study conducted with a 1% CBD cream reported a C_{max} of 8 ng/mL, a T_{max} of 38 h, and a steady-state plasma concentration of 6 ng/mL [445].

2.2.2 Distribution

Distribution of Δ9-THC is time-dependent and begins immediately after absorption. Due to its lipophilicity, it is taken up primarily by fatty tissues and highly perfused organs such as the brain, heart, lung, and liver [78]. Δ9-THC has a large apparent volume of distribution, approximately 10 L/kg, because of its high lipid solubility [446]. The apparent average volume of distribution of CBD is 32.7 L/kg (higher than THC) owing also to its very high lipid solubility [410]. CBN has an even higher volume of distribution, 50 L/kg [447]. The plasma protein binding of Δ9-THC and its metabolites is approximately 97% [448, 449]. Δ9-THC is mainly bound to low-density lipoproteins (LDL), with up to 10% present in red blood cells [450], while the metabolite, 11-hydroxy-THC is strongly bound to albumin with only 1% found in the free-fraction [451].

The highest concentrations of Δ9-THC are found in the heart and in adipose tissue, with levels reaching 10 and 1 000 times that of plasma, respectively [452]. Despite the high perfusion level of the brain, the blood-brain barrier appears to limit the access and accumulation of Δ9-THC in this organ [78, 453, 454], and the delay in correlating peak plasma concentration to psychoactive effects may be attributed, in part, to the time required for Δ9-THC to traverse this barrier [401]. Pre-clinical studies in mice suggest a more rapid penetration of 11-hydroxy-THC into the brain compared to the parent compound, on the order of 6 : 1 for 11-hydroxy-THC to THC [400, 455, 456].

As mentioned, Δ9-THC accumulates and is retained in fatty tissue, and its release from this storage site into the blood is slow [453]. It is also not entirely certain if Δ9-THC persists in the brain (a highly fatty tissue) in the long-term; however, the presence of residual cognitive deficits in abstinent heavy cannabis users suggests this may be the case, at least in the short-term [457, 458]. A study that characterized cannabinoid elimination in blood from 30 male daily cannabis smokers during monitored sustained abstinence for up to 33 days on a closed residential unit found that both THC and its inactive metabolite 11-nor-9-carboxy Δ9-THC were detected in blood up to one month after last smoking, which was reported by the authors as being four times longer than previously described [459]. This finding lends further support to the evidence on the distribution, accumulation, and storage of THC (and metabolites) in the adipose tissue and the slow release of THC (and metabolites) from adipose tissue stores back into the bloodstream [229]. Residual THC in plasma (likely coming from bodily adipose stores) detected weeks after last smoking episode may be associated with persisting psychomotor impairment in frequent chronic cannabis smokers according to the study authors [229]. Lastly, one animal study suggested food deprivation or adrenocorticotropic hormone (ACTH) administration in rats accelerates lipolysis and the release of Δ9-THC from fat stores, however further research is needed to determine if these effects are associated with subsequent intoxication or behavioural/cognitive changes [460].

2.2.3 Metabolism

Most cannabinoid metabolism occurs in the liver, and different metabolites predominate depending on the route of administration [78, 401]. The complex metabolism of Δ9-THC involves allylic oxidation, epoxidation, decarboxylation, and conjugation [401]. Δ9-THC is oxidized by the xenobiotic-metabolizing cytochrome P450 (CYP) mixed-function oxidases 2C9, 2C19, and 3A4 [78]. The major initial metabolites of Δ9-THC are the active 11-hydroxy Δ9-THC, and the non-active 11-nor-9-carboxy Δ9-THC [78]. The psychoactive 11-hydroxy Δ9-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 [461, 462].

CBD undergoes extensive Phase I metabolism, with a reported 30 different metabolites in the urine, and the most abundant metabolites are hydroxylated 7 (or 11)-carboxy derivatives of CBD, with 7 (or 11)-hydroxy CBD as a minor metabolite [78, 463, 464].

CYP isozyme polymorphisms may also affect the pharmacokinetics of THC (and 11-nor-9-carboxy Δ9-THC). For example, subjects homozygous for the *CYP2C9*3* allelic variant displayed significantly higher maximum plasma concentrations of Δ9-THC, significantly higher AUC, and significantly decreased clearance among other measures compared to the *CYP2C9*1* homozygote or the **1/*3* heterozygote [465].

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 [466]. Polyaromatic hydrocarbons found in tobacco and cannabis smoke induce the expression of CYP1A2 [467], while Δ^9-THC, CBD, and CBN inhibit the activity of the CYP1A1, 1A2, 1B1 and 2A6 enzymes [74, 468]. CBD has also been shown to inhibit the formation of Δ^9-THC metabolites catalyzed by CYP3A4, with less effect on CYP2C9 [446], albeit sufficiently to decrease the formation of 11-hydroxy-THC [129, 469]. Please see **Section 6.2** for more detailed information.

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 [74, 431]. 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. nonsteroidal anti-inflammatory agents (NSAIDs), 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, careful monitoring of patients who are concomitantly consuming cannabis/cannabinoids and other medications that are metabolized by the above-mentioned enzymes may be warranted. Please see **Section 6.2** for more detailed information.

The Sativex® product monograph cautions against combining Sativex® with amitriptyline or fentanyl (or related opioids) which are metabolized by CYP3A4 and 2C19 [431]. One clinical study that investigated the effects of rifampicin, ketoconazole, and omeprazole on the pharmacokinetics of THC and CBD delivered from Sativex® reported that co-administration of rifampicin with Sativex® is associated with slight decreases in the plasma levels of THC, CBD and 11-hydroxy-THC, while co-administration of ketoconazole with Sativex® is associated with slight increases in plasma levels of THC, CBD, and 11-hydroxy-THC [470]. No significant effects on plasma levels of THC, CBD or 11-hydroxy-THC were noted with omeprazole.

Cannabis smoking, as well as orally administered dronabinol may also affect the pharmacokinetics of anti-retroviral medications, although no clinically significant short-term impacts on anti-retroviral effects were noted [471]. Concomitant administration of cannabis as a herbal tea (200 mL, 1 g per liter; 18% THC, 0.8% CBD) with 600 mg i.v. irinotecan or 180 mg i.v. docetaxel for 15 consecutive days did not significantly affect the plasma pharmacokinetics of irinotecan or docetaxel [472].

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 [473] or the anti-psychotic medications clozapine or olanzapine [474]. Further detailed 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 [475]. Peak plasma concentrations of 11-hydroxy-THC are approximately 5% to 10% of parent THC, and the AUC profile of this metabolite averages 10 to 20% of the parent THC [462]. Similar results were obtained with intravenous THC administration [476]. Following oxidation, the phase II metabolites of the free drug or hydroxylated-THC appear to be glucuronide conjugates [401].

Peak plasma values of the psycho-inactive metabolite, 11-nor-9-carboxy THC, occur 1.5 to 2.5 h after smoking, and are about one third the concentration of parent THC [475].

2.2.3.2 Oral

In contrast to the limited metabolism of Δ^9-THC to the 11-hydroxy metabolite through pulmonary administration, oral administration of Δ^9-THC results in a significantly greater metabolism of Δ^9-THC to the 11-hydroxy metabolite resulting in similar plasma concentrations of Δ^9-THC and 11-hydroxy Δ^9-THC through the oral route [404, 418, 477]. The plasma levels of active 11-hydroxy metabolite, achieved through oral administration, are about three times higher than those seen with smoking [462]. Furthermore, 11-hydroxy- Δ^9-

THC has been reported to be as psychoactive or even more psychoactive than the parent THC [400, 406, 478-480]. Concentrations of both parent drug and metabolite peak between approximately 2 to 4 h after oral dosing, and decline over several days [481].

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 [227]. 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 [227]. Time to reach C_{max} for 11-hydroxy Δ^9-THC ranged from 30 min to 4 h, with a mean of approximately 2.5 h [227]. As stated above, 11-hydroxy Δ^9-THC has psychotomimetic properties equal to or greater than those of Δ^9-THC [404, 406, 478-480, 482, 483].

2.2.4 Excretion

Δ^9-THC and CBD 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 [484], respectively, and are below 5 ng/mL THC 2 h after smoking, although mean serum THC concentrations may be slightly higher when smoking higher THC potency cigarettes [404]. One study showed that CBD levels fall to below 5 ng/mL in the plasma about 2.5 h after smoking a 19 mg CBD cigarette [410].

Following smoking, elimination of THC and its metabolites occurs via the feces (65%) and the urine (20%) [78]. 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 [227]. The psycho-inactive 11-nor-9-carboxy Δ9-THC is the primary acid metabolite of Δ^9-THC excreted in urine and it [485] is the cannabinoid often screened for in forensic analysis of body fluids [486, 487]. A study that characterized cannabinoid elimination in blood from 30 male daily cannabis smokers during monitored sustained abstinence for up to 33 days on a closed residential unit found that low levels (approx. < 1 ng/mL) of both THC and its inactive metabolite 11-nor-9-carboxy THC were detected in blood up to one month after last smoking, which was reported by the authors as being four times longer than previously described [459].

Following oral administration, THC and its metabolites are also excreted in both the feces and the urine [78, 462]. 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 [462]. Plasma clearance of CBD is similar to that of THC, ranging from 58 to 94 L/h (i.e. 960 – 1560 ml/min) [400, 410]. A large portion of administered CBD is excreted intact or as its glucuronide [463, 488, 489]. Sixteen percent of an administered dose of CBD was recovered in the urine as intact or conjugated CBD within 72 h, while 33% of an administered dose of CBD was recovered mostly unchanged (accompanied by several mono-, di-hydroxylated and mono-carboxylic metabolites) in the feces within 72 h [410, 463].

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 [446]. 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 [78]. 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 [490]. Low levels of THC metabolites have been detected for more than five weeks in the urine and feces of cannabis users [446]. The degree of Δ^9-THC consumption does not appear to influence the plasma half-life of Δ^9-THC [401, 491].

Like THC, the decline of CBD levels is also multi-phasic, and the half-life of CBD in humans after smoking has been estimated at 27 – 35 h, and 2 – 5 days after oral administration [401, 426, 464].

2.3 Pharmacokinetic-pharmacodynamic relationships

Much of the information on cannabinoid pharmacokinetic-pharmacodynamic relationships (mostly on Δ^9-THC) is derived from studies of non-medical 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. But it is known that 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 [128, 211, 490] (See **Section 2.4** *Tolerance and Dependence*).

As mentioned above, the relationship between dose (and plasma concentration) versus response for possible therapeutic applications is ill-defined, except for some information obtained for oral dosing with dronabinol (synthetic Δ^9-THC, marketed as Marinol® but no longer available in Canada), 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 [227, 431, 492]. More limited information is available for inhaled cannabis [58, 59]. Interpretations of the pharmacokinetics of Δ^9-THC are also complicated by the presence of active metabolites, particularly the potent psychoactive 11-hydroxy THC metabolite, which is found in higher concentration after oral administration than after inhalation [418, 477].

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 to 29 ng/mL Δ^9-THC necessary for the production of a 50% maximal subjective "high" effect [490]. 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 intravenous 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) [137, 493]. Notably, impairment of driving performance is seen with plasma concentrations between 7 and 10 ng/mL (whole blood, approximately 3 – 5 ng/mL) and this blood THC concentration has been compared to a blood-alcohol concentration (BAC) of 0.05% which itself is associated with driver impairment [154].

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 [211]. 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 *in the cigarette*, respectively) [149]. 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 an effect on heart rate. Pharmacokinetic-pharmacodynamic modelling of the 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 [494]. The equilibration half-life estimate for heart rate was approximately 7 min, but varied between 39 and 85 min for various CNS parameters [494]. 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 have been studied [409]. 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). During the study, subjects smoked one cannabis cigarette (mean weight 0.79 g) containing 6.8% THC, 0.25% CBD, and 0.21% CBN (w/w) yielding a total THC, CBD, and CBN content of 54, 2.0, and 1.7 mg of these cannabinoids per cigarette. Mean peak THC blood concentrations and peak Visual Analogue Scale (VAS) scores for different subjective measures occurred 15 min after starting smoking. According to the authors of the study, the pharmacodynamic-pharmacokinetic relationship displayed 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. All participants reported a peak subjective "high" between 66 and 85 on the VAS, with peak whole blood THC concentrations at the time of these responses ranging from 13 to 63 ng/mL. 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.

A study that examined the acute subjective effects associated with smoked cannabis at three different doses (i.e. 29.3, 49.1 and 69.4 mg THC) reported that THC significantly increased feelings of "high", "dizziness", "impaired memory and concentration" as well as "down", "sedated" and "anxious" feelings [495]. *In addition, the study also showed that higher doses of THC were associated with longer duration of subjective effects.* Findings from the study showed that the time required to reach a maximal "high" rating was slightly delayed (11 – 16 min) compared to the time required to reach the peak THC serum concentration. The "high" rating declined after reaching the peak within the first 3.5 h post-dose. Scores on the VAS for "dizziness", "dry mouth", "palpitations", "impaired memory and concentration", "down", "sedated", and "anxious feelings" reached a maximum within the first 2 h post-dose and these effects were dose-dependent. With a dose of 29.3 mg THC in the cigarette (equivalent to, for example, a 300 mg joint containing 10% THC or 150 mg of a 20% THC joint), the maximal serum THC concentration was ~120 ng/mL and was associated with a 50% maximal "high". A dose of 49.1 mg THC in the cigarette (equivalent to, for example, a 500 mg joint containing 10% THC or a 250 mg joint containing 20% THC) was associated with a maximal serum THC concentration of 170 ng/mL and a 60% maximal "high". Finally, a THC dose of 69.4 mg of THC (equivalent to, for example, 700 mg of a 10% THC joint or 350 mg of a 20% THC joint) was associated with a serum THC concentration of 200 ng/mL and an 80% maximal "high". The THC-induced decrease in stimulation (i.e. sedation) and increase in anxiety lasted up to 8 h post-smoking. In fact, sedation was increased by almost six-fold compared to placebo. The low THC dose was associated with the highest ratings of "like the effects of the drug" and "want more of this drug".

Vapourized cannabis

Inhalation of vapourized cannabis (900 mg of 3.56% Δ^9-THC; total available dose of 32 mg of Δ^9-THC) 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 [280]. Peak Δ^9-THC concentration (C_{max}) was achieved at 3 min in all study participants. Maximal subjective "high" ratings occurred at 60 min following beginning of inhalation.

One clinical study reported that *ad libitum* vapourization of 500 mg cannabis containing a low-dose (2.9%) of THC (~14.5 mg THC), or high-dose (6.7%) of THC (~33.5 mg THC) was associated with median whole-blood C_{max} values of 32.7 (low-dose) and 42.2 ng/mL (high-dose) THC, and median plasma C_{max} values of 46.5 (low-dose) and 62.1 ng/mL (high-dose) THC at 10 min post-inhalation [206]. Median whole-blood C_{max} values for 11-hydroxy-THC were 2.8 (low-dose) and 5.0 ng/mL (high-dose) and median plasma C_{max} values were 4.1 (low-dose) and 7 ng/mL (high-dose) at 10 – 11 min post-inhalation. Subjective effects were then measured at several time points and effects were correlated with concentrations of cannabinoids in oral fluid and blood. Blood THC was positively associated with "high", "good drug effect", "stimulated", "stoned", "anxious", and "restless" and with feelings of altered time, "slowed/slurred speech", "dizziness", and "dry mouth/throat". There were no significant differences between the effects seen with the low (2.9%) and the high (6.7%) dose of cannabis. Vapourized cannabis significantly increased measures of "stoned" and "sedated" immediately post-dose and lasted 3.3 h (or 4.3 h with the addition of alcohol). Feelings of "anxious" showed significant cannabis-dose effects through 1.4 h. Undesirable effects, including "feeling thirsty" and "dry mouth/throat", increased for the first 3.3 h post-dose. "Difficulty concentrating" and "altered sense of time" produced mixed effects over 2.3 h. Effects and time course of effects were similar between vapourized and smoked cannabis.

Another study measured 17 different psychoactive effects as a function of THC dose and time in vapourized cannabis [276]. In this randomized, double-blind, placebo-controlled clinical study, patients inhaled a total of 8 to 12 puffs of vapourized cannabis containing either 0%, 2.9% or 6.7% THC (400 mg each). The 2.9% dose was associated with a C_{max} of 68.5 ng/mL and the 6.7% dose was associated with a C_{max} of 177.3 ng/mL. Plasma 11-hydroxy-THC C_{max} for the 2.9% dose was 5.6 ng/mL and for the 6.7% dose was 12.8 ng/mL. The lower dose produced effects lower than that for the high dose and placebo effects were lower than both active doses for "any drug effect", "good drug effect", "high", "impaired", "stoned", "sedated" and "changes perceiving space". For "bad drug effect", "like the drug", "nauseous", "changes perceiving time", ratings with placebo were significantly lower than both active doses. The higher dose (6.7%) was associated with significantly higher ratings of "desires more", "hungry", "difficulty remembering things", "drunk", "confused", and "difficulty paying attention" compared with placebo, with only "drunk", "confused" and "difficulty paying attention" significantly different between the high and low dose. There was a clear dose-response effect for the majority of psychoactive effects.

Oral and oro-mucosal cannabinoids

The subjective and physiological effects after controlled administration of oro-mucosal nabiximols (Sativex®) or oral Δ^9-THC have also been compared [122]. 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) oro-mucosal doses of nabiximols, with the effect peaking at around 3 h after administration. 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 oro-mucosal 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. High-dose oral THC (15 mg Δ^9-THC) and high-dose oro-mucosal 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 oro-mucosal nabiximols (5.4 mg Δ^9-THC and 5 mg CBD) was associated with significantly higher "good drug effects" compared to 5 mg THC. 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 oro-mucosal 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 oro-mucosal nabiximols. 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". After high-dose oro-mucosal nabiximols, positive correlations were also observed between plasma THC concentrations and "anxious", "good drug effect", "high", "stimulated", and M-scale (marijuana-scale) scores. 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 CBD did not appear to significantly modulate the effects of THC, the authors suggested it might have attenuated the degree of the subjective "high".

A dose run-up clinical study looking at the pharmacokinetic and pharmacodynamic profile of supratherapeutic oral doses of THC (i.e. 15 mg, 30 mg, 45 mg, 60 mg, 75 mg, 90 mg) in seven cannabis users reported that C_{max} generally increased as a function of dose but varied considerably across subjects, especially at higher doses [496]. There was also substantial variability for T_{max} both within and between subjects with an overall median of 3.3 h for both THC and 11-hydroxy-THC. THC dose-dependently elevated heart rate, and systolic blood pressure dropped at the lower dose (i.e. 30 mg) but increased at higher doses (i.e. 75 mg and 90 mg). No changes were noted for diastolic blood pressure. With regard to subjective responses, "any drug effect" and "thirsty"' ratings increased as a function of dose, however for effects such as "good drug effects", "high", "tired/sedated", "stoned", "forgetful" and "confused/difficulty concentrating" doses larger than 30 mg were not consistently associated with higher ratings.

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 [497].

Tolerance to the effects of cannabis or cannabinoids appears to result mostly from pharmacodynamic rather than pharmacokinetic mechanisms [328]. 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 intracellular downstream signal transduction events), and receptor downregulation (resulting from the internalization and/or degradation of the receptor) [498]. Furthermore, within the brain, these adaptations appear to vary across different regions suggesting cellular- and tissue-specific mechanisms regulating desensitization/downregulation [328]. Studies have reported that CB_1 receptors in the caudate-putamen and its projection areas (e.g. globus pallidus and substantia nigra) show the least magnitude of CB_1 receptor desensitization and downregulation, whereas CB_1 receptors in the hippocampus exhibit the greatest magnitude of desensitization and downregulation in response to chronic THC exposure [499]. CB_1 receptors located in the striatum are also less susceptible to desensitization and downregulation relative to the hippocampus [499].

One clinical study showed that chronic cannabis use was associated with a global decrease in CB_1 receptor availability in the brain with significant decreases in CB_1 receptor availability in the temporal lobe, anterior and posterior cingulate cortices, and the nucleus accumbens [500]. Study subjects were mostly male, had a mean age at onset of cannabis use of 16 years of age, a mean duration of cannabis use of 10 years, a mean amount of cannabis use of three joints per day, and 60% of the study subjects were considered heavy users (several times per day), 30% were moderate users (once per day to 3 – 4 times per week), and 10% used infrequently (two to three times per month or less). Furthermore, a couple of clinical studies have examined the time course of changes in the availability of CB_1 receptors following chronic THC administration and abstinence [334, 501]. In the first study, heavy chronic daily cannabis smoking (average 10 joints/day for average of 12 years) was associated with reversible and regionally selective downregulation (20% decrease) of brain cortical (but not subcortical) cannabinoid CB_1 receptors [501]. In the second study, cannabis dependence (with chronic, moderate daily cannabis smoking) was associated with CB_1 receptor downregulation (i.e. ~15% decrease at baseline, not under intoxication or withdrawal) compared to healthy controls [334]. CB_1 receptor downregulation began to reverse rapidly upon termination of cannabis use (within two days), and after 28 days of continuous monitored abstinence CB_1 receptor availability was not statistically significantly different from that of healthy controls (although

CB_1 receptor availability never reached the levels seen with healthy controls). CB_1 receptor availability was also negatively correlated with cannabis dependence and withdrawal symptoms.

The observed regional variations in cellular adaptations to THC in the brain may also generalize to 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 magnitude and time-course of tolerance appear to depend on the species, the cannabinoid ligand, the dose and duration of the treatment, and the measures employed to determine tolerance to cannabinoid treatment [328].

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 [140]. Tolerance has been reported to develop to the effects of cannabis on perception, psychoactivity, euphoria, cognitive impairment, anxiety, cortisol increase, mood, intraocular pressure (IOP), electroencephalogram (EEG), psychomotor performance, and nausea; some have shown tolerance to cardiovascular effects while others have not [324, 332, 333]. There is also some evidence to suggest that tolerance can develop to the effects of cannabis on sleep (reviewed in [209]). As mentioned above, the dynamics of tolerance vary with respect to the effect studied; tolerance to some effects develops more readily and rapidly than to others [330, 331]. However, tolerance to some cannabinoid-mediated therapeutic effects (i.e. spasticity, analgesia) does not appear to develop, at least in some patients [216, 325, 327]. According to one paper, 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 [502].

One 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; q.i.d. for four days; total daily dose 120 mg) [503] and when a roughly equivalent dose was given by smoking (3.1% THC cigarette; q.i.d. for four days) [504]. There was no diminution of the appetite-stimulating effect from either route of administration. In another study, the intensity of THC-induced acute subjective effect was reportedly decreased by up to 80% after 10 days of oral THC administration (10 – 30 mg THC every 3 – 4 h) [505].

A clinical study that evaluated the effects of smoked cannabis on psychomotor function, working memory, risk-taking, subjective and physiological effects in occasional and frequent cannabis smokers following a controlled smoking regimen reported that when compared to frequent smokers, occasional smokers showed significantly more psychomotor impairment, more significant impairment of spatial working memory, significantly increased risk-taking and impulsivity, significantly higher scores for "high" ratings, for "stimulated" ratings, and more anxiety [181]. Significantly higher scores were reported by occasional than frequent smokers for "difficulty concentrating", "altered sense of time", "feeling hungry", "feeling thirsty", "shakiness/tremulousness", and "dry mouth or throat". Compared with frequent smokers, occasional smokers had significantly increased heart rates relative to baseline and higher systolic and diastolic blood pressure just after dosing. These findings suggest that frequent cannabis users can develop some tolerance to some psychomotor impairments despite higher blood concentrations of THC. Occasional smokers also reported significantly longer and more intense subjective effects compared with frequent smokers who had higher THC concentrations suggesting tolerance can develop to the subjective effects.

A clinical study evaluated the development of tolerance to the effects of around-the-clock oral administration of THC (20 mg every 3.5 – 6 h) over six days, in 13 healthy male daily cannabis smokers [324]. The morning THC dose increased intoxication ratings on day 2 but had less effects on days 4 (after administration of a cumulative 260 mg dose of THC) and 6, while THC lowered blood pressure and increased heart rate over the six-day period suggesting the development of tolerance to the subjective intoxicating effects of THC and the absence of tolerance to its cardiovascular effects. Tolerance to the subjective intoxicating effects of THC administered orally was manifested after a total exposure of 260 mg of THC over the course of four days [324].

Another clinical study reported that while heavy chronic cannabis smokers demonstrated tolerance to some of the behaviourally-impairing effects of THC, these subjects did not exhibit cross-tolerance to the impairing effects of alcohol, and alcohol potentiated the impairing effects of THC on measures such as divided attention [506].

An uncontrolled, open-label extension study of an initial five-week randomized trial of nabiximols in patients with MS and central neuropathic pain reported the *absence* of pharmacological tolerance (measured by a change in the mean daily dosage of nabiximols) to cannabinoid-induced analgesia, even after an almost two-year treatment period in a group of select patients [327]. Another long-term, open-label extension study of nabiximols in patients with spasticity caused by MS echoed these findings, also reporting the *absence* of pharmacological tolerance to the anti-spastic effects (measured by a change in the mean daily dosage of nabiximols) after almost one year of treatment [325]. A multi-centre, prospective, cohort, long-term safety study of patients using cannabis as part of their pain management regimen for chronic non-cancer pain reported small and non-significant increases in daily dose over a one-year study period [216].

More recently, a double-blind, placebo-controlled, three-way cross-over clinical study with regular cannabis users suggested that tolerance may not develop towards some of the acute effects on neurocognitive functions despite regular cannabis use [415]. One hundred and twenty-two subjects who regularly used cannabis (average duration of use: 7 years; range: 1 – 23 years), with an average rate of use of 44 use occasions (range: 2 – 100) over the course of the previous three months, participated in the study. Treatments consisted of vapourized placebo or 300 µg/kg THC (cannabis containing 11 – 12% THC). Acute administration of vapourized cannabis impaired performance across a wide range of neurocognitive domains: executive function, impulse control, attention and psychomotor function were significantly worse after cannabis compared to placebo. Frequency of cannabis use correlated significantly with change in subjective intoxication following cannabis administration and also correlated and interacted with changes in psychomotor performance meaning that subjective intoxication and psychomotor impairment following cannabis exposure decreased with increasing frequency of use, however the baseline for subjective intoxication and psychomotor impairment was already higher for frequent users compared to less frequent users (likely owing to already elevated THC body burden which can cause sufficient levels of intoxication and mild psychomotor impairment). The authors suggest that the neurocognitive functions of daily or near daily cannabis users can be substantially impaired from repeated cannabis use, during and beyond the initial phase of intoxication.

Pharmacokinetic tolerance (including changes in absorption, distribution, biotransformation and excretion) has also been documented to occur with repeated cannabinoid administration, but apparently occurs to a lesser degree than pharmacodynamic tolerance [507].

Dependence and withdrawal

Dependence can be divided into two independent, but in certain situations interrelated concepts: *physical* dependence and *psychological* dependence (i.e. addiction) [497]. 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 [497]. 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 [497]. The ECS 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]. In the former DSM-IV (diagnostic and statistical manual of mental disorders (fourth edition), the term 'dependence' was 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 [508]. There is evidence that cannabis dependence (physical and psychological) occurs, especially with chronic, heavy use [145, 190, 329]. In the new DSM-5, the term "cannabis dependence" has been replaced with the concept of a "cannabis use disorder" (CUD) which can range in intensity from mild to moderate to severe with severity based on the number of symptom criteria endorsed [509]. The DSM-5 defines a CUD as having the following diagnostic criteria: a problematic pattern of cannabis use leading to clinical significant impairment or distress, as manifested by at least two symptoms, occurring within a 12-month period. For a list of symptoms, please refer to the DSM-5 [509]**.**

Psychological dependence

Risk factors for transition from use to dependence have been identified and include being young, male, poor, having a low level of educational attainment, urban residence, early substance use onset, use of another psychoactive substance, and co-occurrence of a psychiatric disorder [510]. Notably, the transition to cannabis dependence occurs considerably more quickly than the transition to nicotine or alcohol dependence [510]. It has been reported that after the first year of cannabis use onset, the probability of transition to dependence is almost 2%, while the lifetime prevalence of cannabis dependence among those who ever used cannabis is approximately 9% [510]. The prevalence of developing a CUD increases to between 33 and 50% among daily users [511]. More recent U.S. epidemiological data suggest that 12-month and lifetime prevalence of DSM-5 CUD was 2.5% and 6.3% respectively, and the corresponding DSM-IV 12-month and lifetime rates showed a substantial increase between 2001 – 2002 and 2012 – 2013 increasing from 12-month and lifetime rates of 1.5% and 8.5% respectively to 2.9% and 11.7% respectively [338]. These increases in both 12-month and lifetime prevalence are thought to be driven by increases in the prevalence of cannabis users.

The **N**ational **E**pidemiological **S**urvey on **A**lcohol and **R**elated **C**onditions (**NESARC**), a large U.S. national prospective study conducted among 34 653 respondents examining the association between cannabis use and risk of mental health and substance use disorders in the U.S. general adult population, reported that cannabis use (at Wave 1, 2001 – 2002) was associated with later development (at Wave 2, 2004 – 2005) of substance use disorders (i.e. any substance use disorder: OR = 6.2, 95% CI = 4.1 – 9.4; any alcohol use disorder: OR = 2.7, 95% CI = 1.9 – 3.8; any CUD: OR = 9.5, 95% CI = 6.4 – 14.1; any other drug use disorder: OR = 2.6, 95% CI = 1.6 – 4.4; and nicotine dependence: OR = 1.7; 95% CI = 1.2 – 2.4), but not any mood disorder or anxiety disorder [512]. Higher frequency of cannabis use was associated with greater risk of disorder incidence and prevalence, supporting a dose-response association between cannabis use and risk of substance use disorders.

Another study using the U.S. **NESARC** data (2012 – 2013) found that the odds of 12-month and lifetime CUD were higher for men, Native Americans, unmarried individuals, those with low incomes, and young adults (e.g. among those 18 – 24 years of age compared to those over 45, OR = 7.2, 95% CI = 5.5 – 9.5) [338]. Furthermore, 12-month CUD was associated with other substance use disorders (OR = 6.0 – 9.3), affective/mood disorders (OR = 2.7 – 5.0), anxiety disorders (OR = 1.7 – 3.7), and personality disorders (OR = 3.8 – 5.0). Survey respondents with 12-month CUD differed significantly from others on all disability components of the survey, with disability increasing significantly, as cannabis disorder severity increased. Among participants with 12-month DSM-5 CUD, 61% had craving for cannabis, 32% had cannabis withdrawal symptoms, and 23% had both.

Comparing data between the **NESARC** 2001 – 2002 (Wave 1) and 2012 – 2013 (Wave 2), one study reported that the prevalence of cannabis use more than doubled between the two waves of the survey [513]. Furthermore, there was a large increase in CUD during this intervening time, with nearly 3 out of 10 cannabis users reporting a CUD in 2012 – 2013. Young adults were at highest risk of CUD in both survey waves (OR = 7.2 for ages 18 – 29; OR = 3.6 for ages 30 – 44) however, the relative increases in prevalence of CUD among adults aged 45 to 64 years and 65 years and older were much greater than the increases in young adults.
A retrospective study among a nationally representative sample of 6 935 Australian adults examining the initiation of cannabis use and transition to CUD found that the mean time from first use to the onset of CUD was 3.3 years (median time = 2 years), with 90% of cases manifesting within eight years [514]. Younger age of initiation and other substance use were strong predictors of the transition from use to CUD. In fact, younger age of first cannabis use was associated with increased risk of transition to CUD, with each year older at first use associated with 11% lower odds of onset of CUD. Social phobia and panic disorder were also associated with transition from cannabis use to CUD. Male cannabis users had greater risk of CUD than female users, but among women, those with depression were more likely to develop a CUD. Early-onset of alcohol and daily cigarette smoking were each associated with marked increased risk of early initiation of cannabis use.

A handful of clinical studies have examined the differences between men and women with respect to development of dependence, withdrawal symptoms and relapse [515]. See **Section 2.5**, *Sex-dependent effects* for additional information.

Physical dependence
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 one to two weeks [516-518]. The most common symptoms include craving, anger or aggression, irritability, anxiety, nightmares/strange dreams, insomnia/sleep difficulties, headache, restlessness, and decreased appetite or weight loss [190, 329, 342, 516, 517]. Other symptoms appear to include depressed mood, chills, stomach pain, shakiness and sweating [190, 329, 342, 517]. Withdrawal symptoms are reported by up to one-third of regular users in the general population and by 50 – 95% in heavy users in treatment or in research studies [519]. Cannabis withdrawal symptoms appear to be moderately inheritable with both genetic and environmental factors at play [519]. There are also emerging reports of increased physical dependence with highly potent cannabis extracts (e.g. concentrates such as butane hash oil and dabs) (OR = 1.2, $p = 0.014$) [520, 521].

There are no approved pharmacotherapies for managing cannabis withdrawal symptoms [522]. A range of medications have been explored including antidepressants (e.g. buproprion, nefadozone) [523, 524], mood stabilizers (e.g. divalproex, lithium, lofexidine) [525-527], and quetiapine [528] but only limited benefits have been observed [522]. Zolpidem has also been explored as a potential pharmacotherapy to specifically target abstinence-induced disruptions in sleep [529, 530]. However, agonist substitution therapy (e.g. dronabinol, nabilone, nabiximols) may be a more promising approach [522].

A pilot clinical study that measured the feasibility/effects of fixed and self-titrated dosages of nabiximols on craving and withdrawal among cannabis-dependent subjects found that high fixed dosages of nabiximols (i.e. up to 40 sprays per day or 108 mg THC and 100 mg CBD) were well tolerated and significantly reduced cannabis withdrawal symptoms during abstinence, but not craving, compared to placebo [339]. Self-titrated doses were lower and showed limited efficacy compared to high fixed doses and subjects typically reported significantly lower ratings of "high" and shorter duration of "high" with nabiximols and placebo compared to smoking cannabis.

A randomized, double-blind, placebo-controlled, six-day, inpatient clinical study of nabiximols as an agonist replacement therapy for cannabis withdrawal symptoms reported that nabiximols treatment attenuated cannabis withdrawal symptoms and improved patient retention in treatment [522]. However, placebo was as effective as nabiximols in promoting long-term reductions in cannabis use at follow-up. Nabiximols treatment significantly reduced the overall severity of cannabis withdrawal symptoms relative to placebo including effects on irritability, depression and craving as well as a more limited effect on sleep disturbance, anxiety, appetite loss, physical symptoms and restlessness.

A placebo-controlled, within-subject, clinical study demonstrated that nabilone (6 – 8 mg daily) decreased cannabis withdrawal symptoms including abstinence-related irritability and disruptions in sleep and food intake in daily, non-treatment seeking cannabis smokers [531]. It also decreased cannabis self-administration during abstinence in a laboratory model of relapse. While nabilone did not engender subjective ratings associated with abuse liability (i.e. drug liking, desire to take again), the high dose (8 mg) modestly decreased psychomotor task performance. A follow-up study found that nabilone (3 mg, b.i.d.) co-administered with zolpidem (12.5 mg) also ameliorated abstinence-induced disruptions in mood, sleep, and appetite, decreased cannabis smoking in the laboratory model of relapse, and did not affect cognitive performance [529].

A double-blind, placebo-controlled, 11-week clinical trial testing lofexidine and dronabinol for the treatment of CUD reported no significant beneficial effect compared to placebo for promoting abstinence, reducing withdrawal symptoms, or retaining individuals in treatment [532] in contrast to a previous study that showed efficacy of 40 mg dronabinol daily vs. placebo in alleviating withdrawal symptoms and improving treatment retention but not abstinence [533].

Cannabidiol for cannabis and other drug dependence

A recent systematic review of the evidence of CBD as an intervention for addictive behaviours reported that to date, only 14 studies have been conducted, the majority in animals with only a handful in humans [341]. The limited number of pre-clinical studies carried out to date suggest that CBD may have therapeutic potential for the treatment of opioid, cocaine and psychostimulant addiction, and some preliminary data suggest CBD may also be beneficial in cannabis and tobacco addiction in humans [341]. The limited number of pre-clinical studies published thus far suggest CBD may have an impact on the intoxication and relapse phase of opioid addiction, while CBD does not appear to have an impact on the rewarding effects of stimulants (e.g. cocaine, amphetamine) but may affect relapse [341].

With respect to cannabis dependence, pre-clinical studies show that CBD is not reinforcing on its own, but its impact on cannabis-related dependence behaviour remains unclear [341]. In one clinical study, a 19 year-old female with cannabis dependence exhibiting cannabis withdrawal symptoms upon cannabis cessation was administered up to 600 mg of CBD (range: 300 – 600 mg) over the course of an 11-day treatment period and CBD treatment was associated with a rapid decrease in withdrawal symptoms [341, 534]. In another human study, cannabis with a higher CBD to THC ratio was associated with lower ratings of pleasantness for drug stimuli (explicit "liking"), but no group difference in "craving" or "stoned" ratings was noted [341, 535]. However, a multi-site, double-blind, placebo-controlled study demonstrated that CBD (200 – 800 mg) had no effect on subjective ratings associated with cannabis abuse liability [536].

A randomized, double-blind, placebo-controlled clinical study of 24 tobacco smokers seeking treatment for tobacco dependence investigated the impact of CBD on nicotine addiction and found that inhalation of CBD (400 µg/inhalation), as needed, was associated with a significant reduction in the number of cigarettes smoked [341, 537].

A randomized, double-blind, crossover clinical study in 10 healthy volunteers examining the effects of CBD on the intoxication phase of alcohol addiction reported no differences in feelings of "drunk", "drugged", or "bad" between the alcohol only and the alcohol and CBD groups [341, 538].

No pre-clinical studies exist on the use of CBD for hallucinogen-, sedative-, tobacco-, or alcohol-addictive behaviours and no human studies exist on the use of CBD for opioid-, psychostimulant-, hallucinogen-, or sedative-addictive behaviours [341].

2.5 Special populations

Pediatric/Adolescent

The ECS is present in early development, is critical for neurodevelopment and maintains expression in the brain throughout life [539]. Furthermore, the ECS undergoes dynamic changes during adolescence with significant fluctuations in both the levels and locations of the CB_1 receptor in the brain as well as changes in the levels of the endocannabinoids 2-AG and anandamide [539]. The dynamic changes occurring in the ECS during adolescence also overlap with a significant period of neuronal plasticity that includes neuronal proliferation, rewiring and synaptogenesis, and dendritic pruning and myelination that occurs at the same time [540]. This period of significant neuroplasticity does not appear to be complete until at least the age of 25 [540]. Thus, this neurodevelopmental time window is critical for ensuring proper neurobehavioural and cognitive development and is also influenced by external stimuli, both positive and negative (e.g. neurotoxic insults, trauma, chronic stress, drug abuse) [540]. Based on the available scientific evidence, youths are more susceptible to the adverse effects associated with cannabis use, especially chronic use [182, 541]. Studies examining non-medical use of cannabis strongly suggest early onset (i.e. in adolescence and especially before age 15), regular and persistent cannabis use (of THC-predominant cannabis) is associated with a number of adverse effects on brain and behavioural development including CUD and addiction, other illicit drug use, compromised cognitive functioning and decreased IQ, deficits in attention, poorer educational attainment, suicidal ideation, suicide attempt, and increased risk of schizophrenia as well as an earlier onset of the latter disease [151, 542-552]. Based on the current available evidence, it is unclear for how long some or all of the neurocognitive effects persist following cessation of use. Some investigators have found certain cognitive deficits to persist for up to one year or longer after cannabis cessation, while others have demonstrated a far shorter period of recovery (i.e. 28 days) for at least some of the evidenced deficits [150, 151, 552-554]. A recent literature review of observational and pre-clinical studies revealed consistent evidence of an association between adolescent cannabis use (frequent/heavy use) and persistent adverse neuropsychiatric outcomes in adulthood. Though the data from human studies do not establish causality solely from cannabis use, the pre-clinical studies in animals do indicate that adolescent exposure to cannabinoids can catalyze molecular processes leading to functional deficits in adulthood – deficits that are not found following adult exposure to cannabis. The authors note that definitive conclusions cannot be made yet as to whether cannabis use – on its own – negatively impacts the adolescent brain, and future research can help elucidate this relationship by integrating assessments of molecular, structural, and behavioral outcomes [555]. Factors that may influence persistence of cognitive deficits can include age at onset of use, frequency and duration of use, co-morbidities, and use of other drugs (tobacco, alcohol, and other psychoactive drugs).

While adverse effects associated with THC-predominant cannabis use in youth have been well documented, far less is known about the adverse effects associated with CBD-predominant cannabis use. Nevertheless, as mentioned above, the ECS plays important roles in nervous system development *in utero* as well as during youth (see **Section 7.4**) and exposure to exogenous cannabinoids, especially at higher doses, on a daily basis and over a protracted period of time may alter the course of neurodevelopment (see **Section 1.0** for additional information on the role of the ECS in the development of the nervous system).

Geriatric

There is evidence to suggest that like the changes seen with the ECS during development and adolescence, there are changes in the ECS associated with ageing. In rodents, there is a marked decline in the levels of CB_1 mRNA and/or specific binding of CB_1 agonists in the cerebellum, cortex, hippocampus and hypothalamus of older animals [556]. In addition, the coupling of CB_1 receptors to G proteins is also reduced in specific brain areas in older animals [556]. Age-related changes in the expression of components of the ECS appear similar in rodents and humans [556]. Disruption of CB receptors appears to enhance age-related decline of a number of tissues suggesting an important role for the ECS in the control of the ageing process [556].

In general, the elderly may be more sensitive to the effects of drugs acting on the CNS [557]. A number of physiological factors may lie at the root of this increased sensitivity such as: (1) age-related changes in brain volume and number of neurons as well as alterations in neurotransmitter sensitivity which can all increase the pharmacological effects of a drug; (2) age-related changes in the pre- and post-synaptic levels of certain neurotransmitter receptors; (3) age-related changes in the sensitivity of receptors to neurotransmitters; and (4) changes in drug disposition in the elderly being generally associated with higher concentrations of psychotropic drugs in the CNS. There is very little information available on the effects of cannabis and cannabinoids in geriatric populations and based on current levels of evidence, no firm conclusions can be made with regard to the safety or efficacy of cannabinoid-based drugs in elderly patients (but see below for one of the few clinical studies of safety carried out specifically in geriatric populations) [421, 557, 558]. Furthermore, as cannabinoids are lipophilic, they may tend to accumulate to a greater extent in elderly individuals since such individuals are more likely to have an increase in adipose tissue, a decrease in lean body mass and total body water, and an increase in the volume of distribution of lipophilic drugs [557]. Lastly, age-related changes in hepatic function such as a decrease in hepatic blood flow and slower hepatic metabolism can slow the elimination of lipophilic drugs and increase the likelihood of adverse effects [557].

Clinical Studies

A randomized, double-blind, placebo-controlled, cross-over clinical trial that evaluated the *pharmacokinetics* of THC in 10 older patients with dementia (mean age 77 years) over a 12-week period reported that the median time to reach maximal concentration in the blood (T_{max}) was between 1 and 2 h with THC pharmacokinetics increasing linearly with increasing dose but with wide inter-individual variation [421]. Patients received 0.75 mg THC twice daily over the first six weeks and 1.5 mg THC twice daily over the second six-week period. The mean C_{max} after the first 0.75 mg THC dose was 0.41 ng/mL and after the first 1.5 mg THC dose was 1.01 ng/mL. After the second dose of 0.75 mg THC or 1.5 mg THC, the C_{max} was 0.50 and 0.98 ng/mL respectively.

Only one clinical study has thus far been carried out looking specifically at the *safety* of THC in an elderly population. This phase I, randomized, double-blind, double-dummy, placebo-controlled, cross-over trial of three single oral doses of Namisol®, a novel tablet form of THC (i.e. 3 mg, 5 mg, 6.5 mg THC) [180] reported that, overall, the pharmacodynamic effects of THC in healthy older individuals were smaller than effects previously reported in young adults and that THC, at the doses tested, appeared to be well-tolerated by healthy older individuals [180]. In this study, 12 adults aged 65 and older who were deemed to be healthy were included, and exclusion criteria included high falls risk, regular cannabis use, history of sensitivity to cannabis, drug and alcohol abuse, compromised cardiopulmonary function, and psychiatric comorbidities. The most commonly reported health problems were hypertension and hypercholesterolemia and subjects reported using an average of 2 medications (e.g. lipid-lowering drugs, aspirin, and beta-blockers). The most frequently reported adverse effects associated with THC were drowsiness (27%), dry mouth (11%), coordination disturbance (9%), headache (9%), difficulties concentrating (7%), blurred vision (5%), relaxation, euphoria and dizziness (5% each); nausea, dry eyes, malaise and visual hallucinations were all reported at a frequency of 2% in this trial. Adverse events first occurred within 20 min of dosing, with all adverse events occurring between 55 and 120 min after dosing and resolving completely within 3.5 h after dosing. There appeared to be a dose-dependent increase in the number of individuals reporting an increased number of adverse events with increasing doses of Namisol®. No moderate or serious adverse events were reported in this trial. While this clinical study adds important information regarding the safety and tolerability of THC in a healthy elderly population, additional studies are needed to evaluate the safety and tolerability of cannabis and cannabinoids in elderly populations having various co-morbidities.

Sex-dependent effects

In humans, sex-dependent differences have been often observed in the biological and behavioural effects of substances of abuse, including cannabis [559]. In male animals, higher densities of CB_1 receptors have been observed in almost all cerebral regions analyzed whereas in females a more efficient coupling of the CB_1 receptor to downstream G-protein signaling has been observed [560]. In humans, sex differences in CB_1 receptor density have also been reported, with men having higher receptor density compared to women [561]. Sex-dependent differences have also been noted with respect to cannabinoid metabolism. Pre-clinical studies in females report increased metabolism of THC to 11-hydroxy-THC compared to males where THC was also biotransformed to at least three different, less active metabolites [562]. There is also evidence to suggest that effects of cannabinoids vary as a function of fluctuations in reproductive hormones [515, 563]. Together, these findings suggest that the neurobiological mechanism underlying the sex-dependent effects of cannabinoids may arise from sexual dimorphism in the ECS and THC metabolism, but also from the effects of fluctuations in hormone levels on the ECS [515, 563].

There is also evidence to suggest sex-dependent differences in subjective effects and development of dependence, withdrawal symptoms, relapse and incidence of mood disorders. Data combined from four double-blind, within-subject studies measuring the effects of smoked “active” cannabis (3.27 – 5.50% THC) against smoked “inactive” cannabis (0.0 % THC) showed that, when matched for cannabis use (i.e. near-daily), women reported higher ratings of abuse-related effects relative to men under “active” cannabis conditions but did not differ in ratings of intoxication [515]. These findings suggest that, at least among near-daily cannabis users, women may be more sensitive to the subjective effects of cannabis, especially effects related to cannabis abuse liability compared to men. Another study demonstrated dose-dependent sex differences in subjective responses to orally administered THC [564]. In this study, women showed greater subjective effects at the lowest dose (5 mg), whereas men showed greater subjective responses at the highest (15 mg) dose. Together, these studies suggest that while women may be more sensitive to the subjective effects of THC at lower doses, they may develop tolerance to these effects at higher doses, which could, for example, have implications for the development of dependence. For example, while cannabis use among men is more prevalent and men appear to be more likely than women to become dependent on cannabis, women tend to have shorter intervals between the onset of use and regular use or development of dependence (commonly referred to as the “telescoping effect”) [565]. In addition, women abstaining from cannabis use reported more withdrawal symptoms, with some being more severe, than those seen in men and which have been linked to relapse [566, 567]. Women with CUD also present with higher rates of certain comorbid health problems such as mood and anxiety disorders [170, 568, 569].

3.0 Dosing

The College of Family Physicians of Canada, along with other provincial medical regulatory colleges, has issued a guidance document (in 2018) for authorizing the use of cannabis for medical purposes. Please consult these and any other official guidance documents, as applicable, for additional information regarding dosing and other matters associated with authorizing cannabis for medical purposes.

Cannabis has many variables that do not fit well with the typical medical model for drug prescribing [405]. The complex pharmacology of cannabinoids, inter-individual (genetic) differences in cannabinoid receptor structure and function, inter-individual (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 varying amounts and ratios of different cannabinoids, 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) [405, 484].

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, varies with the ingested matrix (e.g. fat content), 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, however, some preliminary data has emerged for dosing with cannabis oils [137, 418, 422, 570, 571]. Other forms of preparation reported in the lay literature include cannabis-based butters, candies, edibles, oils, compresses, creams, ointments, and tinctures [80, 572-575] but again, limited dosing information exists here with much of the information being anecdotal in nature.

Dosing remains highly individualized and relies largely on titration [405]. Patients with no prior experience with cannabis and initiating cannabis therapy for the first time are cautioned to begin at the very lowest dose and to stop therapy if unacceptable or undesirable side effects occur. Consumption of smoked/inhaled or oral cannabis should proceed slowly, waiting a minimum of 10 – 20 minutes between puffs or inhalations and waiting a very minimum of 30 minutes, but preferably 3 h, between bites of cannabis-based oral products (e.g. cookies, baked goods) to gauge for strength of effects or for possible overdosing. Subsequent dose escalation should be done slowly, once experience with the subjective effects is fully appreciated, to effect or tolerability. If intolerable adverse effects appear without significant benefit, dosing should be tapered and stopped. Tapering guidelines have not been published, but the existence of a withdrawal syndrome (see Section 2.4) suggests that tapering should be done slowly (i.e. over several days or weeks).

Minimal therapeutic dose and dosing ranges

Clinical studies of cannabis and cannabis-based products for therapeutic purposes are limited to studies carried out with dried cannabis that was smoked or vapourized and with synthetic or natural cannabis-based products that have received market authorization (i.e. dronabinol, nabilone, and nabiximols). With the possible exception of trials conducted with Epidiolex® (CBD-enriched oil) for epilepsy [576, 577] and one open-label pilot clinical trial of oral THC oil for symptoms associated with post-traumatic stress disorder (PTSD) [571] there are no other clinical studies of fresh cannabis or cannabis oils for therapeutic purposes. As such, providing precise dosing guidelines for such products is not possible although existing sources of information can be used as a reference point (see below).

Prescription cannabinoids

Information obtained from the monograph for Marinol® (dronabinol; no longer available in Canada) 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 to 40 mg Δ^9-THC/day (maximal tolerated daily human dose = 210 mg Δ^9-THC/day) [227]. Average daily dose of dronabinol is 20 mg and maximal recommended daily dose is 40 mg [227]. Doses less than 1 mg of THC per dosing session may further avoid incidence and risks of adverse effects. **Dosing ranges for Cesamet® (nabilone) vary from 0.2 mg to 6 mg/day** [492, 578]. **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 and 40 mg CBD) per day** [284, 431]. Information from clinical studies with Epidiolex®, an oil-based extract of cannabis containing 98% CBD, suggests a daily dosing range between 5 and 20 mg/kg/day [263, 576]. For additional information on dosing, please see the [Access to Cannabis for Medical Purposes Regulations - Daily Amount Fact Sheet (Dosage)](#).

Survey and clinical data

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 and 20 g of cannabis per week or approximately 1 to 3 g of cannabis per day [225, 405, 579].

An international, web-based, cross-sectional survey examining patients' experiences with different methods of cannabis intake reported that from among a group of 953 self-selected participants, from 31 countries, the vast majority preferred inhalation over other means of administration (e.g. teas, foods, prescription cannabinoid medications) for symptoms such as chronic pain, anxiety, loss of appetite, depression, and insomnia or sleeping disorder. Mean daily doses with smoked or vapourized cannabis were 3.0 g (median for smoked cannabis was 2 g per day; for vapourized cannabis it was 1.5 g per day) [580]. With foods/tinctures, mean daily dose was 3.4 g (median was 1.5 g per day), and with teas the mean daily dose was 2.4 g (median 1.5 g). Information regarding cannabinoid potencies of cannabis products (i.e. THC/CBD levels) was not available. Daily frequency of use for smoking was six times per day, whereas with vapourizing it was five times per day. Teas and food/tinctures were used on average twice per day. First onset of effects for smoking were noted on average around 7 min after start of smoking, 6.5 min after start of vapourizing, 29 min after ingestion of tea, and 46 min after ingestion of foods/tinctures. Other data suggests that those patients who use cannabis for medical purposes use up to one gram or less per day. For example, data from the Netherlands suggests the average daily dose of dried cannabis for medical purposes stood at 0.68 g per day (range: 0.65 – 0.82 g per day), whereas information obtained from the Israel medical cannabis program in 2016 suggests the average daily amount used by patients was slightly under 1.5 g (Health Canada personal communication). Canadian market data collected from licensed producers under the Access to Cannabis for Medical Purposes Regulations (ACMPRs) showed that, from April 2017 to March 2018, clients had been authorized by their healthcare practitioners to use, monthly, an average of 2.1-2.5 g/day of dried cannabis. However, since this data is collected per licensed producer, it does not include cases where clients split their authorization into two or more authorizations in order to register with more than one licensed producer at a time or personal production registrations with Health Canada [581]. There is no specific data on the average amount of oil authorized by healthcare practitioners since authorized amounts are always in g/day. To fulfill orders for oils, licensed producers equate oil to dried cannabis based on the formulation of their oil products. On average, licensed producers equate 1 g of dried cannabis to 6.6 g of oil. Using this average conversion factor, healthcare practitioners have authorized an equivalent average of 13.9-16.5 g/day of oil.

Satisfaction ratings for criteria such as onset of effects and ease of dose finding were reported to be higher for smoking and vapourizing (i.e. smoking/vapourizing favoured) over other means of administration [580]. However, prescription cannabinoid medications (e.g. dronabinol, nabilone, nabiximols) scored similarly to foods/tinctures and teas on satisfaction ratings related to daily dose needed, and ease of dose finding. Satisfaction ratings in terms of side-effects were higher for non-prescription unregulated cannabis products, with the inhaled route rated best, although the survey did not ask specific questions about the types of side effects. Satisfaction ratings were only slightly higher for orally ingested cannabis products for criteria such as duration of effects. Satisfaction ratings in terms of costs were slightly higher for smoking/vapourizing, teas, and foods/tinctures compared to prescription cannabinoid medications. Satisfaction ratings in terms of ease of preparation and intake were lowest for teas and foods/tinctures. The majority of survey participants had indicated having used cannabis products prior to onset of their medical condition.

A prospective, open-label, longitudinal study of patients with treatment resistant chronic pain reported that patients titrate their cannabis dose starting with one puff or one drop of cannabis oil per day, increasing in increments of one puff or one drop of oil per dose, three times per day until satisfactory pain relief was achieved or side effects appeared [582]. THC concentrations in the smoked product ranged between 6 – 14 % THC and between 11 – 19 % in the oral oil formulations, with CBD concentrations between 0.2 – 3.8 % in the smoked product and 0.5 – 5.5 % in the oral oil formulation. Mean monthly prescribed amount of cannabis was 43 g or 1.4 g/day.

Data from randomized, double-blind, placebo-controlled clinical studies of smoked or vapourized cannabis used a daily dose of up to 3.2 grams of dried cannabis of varying potencies (range: 1 – 23 % THC; see Table 5).

Data from a pilot clinical trial with the Syqe Inhaler™ has shown that an inhaled (vapourized) dose of 3 mg THC (delivered from an amount as low as **15 mg** of dried cannabis plant material at a potency of 20% THC; actual dose absorbed 1.5 mg THC) was associated with analgesic efficacy with minimal adverse effects [58]. In contrast to the gram amounts of cannabis used with smoked, vapourized, and oral routes of administration, the mean daily amounts for prescription cannabinoids such as dronabinol were 30 mg, for nabilone 4.4 mg, and for nabiximols 46 mg THC and 43 mg CBD (i.e. 17 sprays).

Taken together, data from patient surveys and clinical studies suggests that most patients use up to 3 g of dried cannabis per day for medical purposes, although much less (< 1 g/day) can be used with apparent efficacy and decreased incidence of side-effects.

Dosing and threshold of psychotropic effects
With respect to the relationship between **dosing** and **psychotropic effects**, it has been estimated that an inhaled dose of 0.045 – 0.1 mg/kg of THC (i.e. an individual inhaled dose of 3 – 6 mg THC) would be sufficient to reach the threshold for psychotropic effects, with an inhaled dose of 0.15 – 0.3 mg/kg THC (i.e. an individual inhaled dose of 10 – 20 mg THC) being sufficient to produce marked intoxication [415, 583]. Furthermore, it has been estimated that between one and three puffs of higher potency cannabis would be sufficient to produce significant psychoactive effects [495]. One study has shown that while cannabis smokers titrate their dose of THC by inhaling lower volumes of smoke when smoking "strong" joints (i.e. "skunk", > 15% THC), this did not fully compensate for the higher THC doses per joint when using "strong" cannabis and therefore users of more potent cannabis are exposed to greater quantities of THC [584]. For oral administration, a dose of 0.15 – 0.3 mg/kg of THC (i.e. an individual oral dose of 10 – 20 mg THC) would be sufficient to reach the threshold for psychotropic effects and a dose of 0.45 – 0.6 mg/kg of THC (i.e. an individual oral dose of 30 – 40 mg of THC) would be sufficient to produce marked intoxication [415, 583, 585].

Monitoring and clinical practice guidelines
The College of Family Physicians of Canada has published a guidance document describing a patient monitoring strategy/approach for physicians considering authorizing the use of marijuana for medical purposes [586]. Other provincial bodies may also provide guidelines on monitoring [275]. The College of Family Physicians of Canada has recently published a simplified guideline for prescribing medical cannabinoids in primary care [587].

Beaulieu et al. have elaborated recommendations for physicians with respect to the evaluation and management of patients that could be candidates for cannabis/cannabinoids [275]. The recommendations are as follows:

Table 2. Recommendations for the Evaluation and Management of Patients

(1) **Take** a medical history and **perform** a physical examination
(2) **Assess** symptoms to be treated, **identify** any active diagnoses, and **ensure** patients are under optimal management
(3) **Assess** psychological contributors and risk of addiction or substance abuse
(4) **Document** any history or current use of illicit or non-prescribed drugs, including cannabis and synthetic cannabinoids
(5) **Determine** the effect of previous use of cannabinoids for medical purposes
(6) **Consider** a urinary drug screening to assess current use of prescribed and non-prescribed medications
(7) **Set** goals for treatment with cannabis – e.g., pain reduction, increased functional abilities, improved sleep quality, increased quality of life, reduced use of other medications
(8) **Develop** a treatment plan incorporating these goals
(9) **Discuss** likely and possible side effects that might be experienced with cannabis/cannabinoid use
(10) **Discuss** the risks of addiction
(11) **Develop** a follow-up schedule to monitor the patient
(12) **Determine** whether the goals of treatment are being achieved and the appropriateness of the response
(13) **Monitor** for potential misuse or abuse (being aware of clinical features of cannabis dependence)
(14) **Develop** a treatment strategy, particularly for patients at risk
(15) **Maintain** an ongoing relationship with the patient

3.1 Smoking

According to the World Health Organization (WHO) [588], a typical joint contains between 500 mg 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 3**), and in CBD content between 0 and 180 mg (i.e. between 0 and 24%). The majority of clinical trials with smoked cannabis for medical purposes have used joints of dried cannabis weighing between 800 and 900 mg. Estimates that are more recent suggest the mean weight of cannabis in a joint is 320 mg [589]. The gram amount of *cannabis plant material* combusted in a "typical" puff has been estimated to range between 25 and 50 mg/puff, although amounts as high as 160 mg/puff have been noted [59, 143, 403, 583, 590].

The actual amount of Δ^9-THC delivered in the smoke varies widely and has been estimated at 20 to 70%, the remainder being lost through combustion or side-stream smoke [405]. 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 highly variable (2 – 56%) and influenced by the smoking topography (i.e. the number, duration, and spacing of puffs, hold time and inhalation volume) [404]. In addition, expectation of drug reward can also influence smoking dynamics [591]. 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 [141, 405, 592].

Relationship between a smoked/vapourized dose and an oral dose

Little reliable information exists regarding conversion of a "smoked dose" of THC to an equivalent oral dose. However, based *solely* on measures of bioavailability, 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%), ~ three-fold difference between inhaled and oral routes) can yield an approximately equivalent oral dose of Δ^9-THC [141, 583, 592]. However, it is important to point out that these studies did not accurately measure the exact smoked dose of Δ^9-THC that was delivered, and as such remains a very rough approximation. It is also important to emphasize that this "conversion factor" appears to relate mostly to psychoactive effects (e.g. euphoria, feeling mellow, feeling a good drug effect, feeling sedated, feeling stimulated, Addiction Research Center Inventory marijuana scale), psychomotor performance, and food intake and is based on a very small number of comparative pharmacology studies [137, 592, 593]. Further rigorous comparative pharmacology studies are required. In addition, no comparative studies have been done with vaping. In addition, this *theoretical* conversion factor may or may not apply for therapeutic effects. Indeed, it is important to highlight that two studies reported that individuals using cannabis for therapeutic purposes indicated they used approximately similar gram amounts of cannabis **regardless** of route of administration [216, 580].

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

There are a small number of efficacy studies on the amounts of smoked/vapourized cannabis and plasma concentrations of Δ^9-THC required for therapeutic effects (see **Table 5** 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 [59]. The study reported improvements in sleep and pain relief in patients suffering from chronic neuropathic pain with minimal/mild psychoactive effects.

A single-dose, open-label, clinical trial of patients with neuropathic pain and using very low doses of inhaled THC reported a statistically significant improvement in neuropathic pain with minimal adverse effects [58]. In this clinical study, 10 patients suffering from neuropathic pain of any type were administered a vapourized dose of 3 mg of THC (available in the device; ~ 1.5 mg THC actually absorbed) resulting from vapourization of 15 mg of dried cannabis containing 20% THC. THC administration was associated with a statistically significant reduction in baseline VAS for pain intensity of 3.4 points (i.e. a 45% reduction in pain) within 20 min of inhalation, which returned to baseline within 90 min. THC was detected in blood within 1 min following inhalation and reached a maximum within 3 min at a mean THC concentration of 38 ng/ml and there were minimal/mild psychoactive effects.

A randomized controlled clinical trial of vapourized cannabis for the alleviation of pain and spasticity associated with spinal cord injury (SCI) and disease reported that median blood plasma concentrations of THC of 23 ng/mL (from vapourization of 46 mg of 2.9% low THC strength cannabis; estimated 1.3 mg THC inhaled) and 47 ng/mL (from vapourization of 56 mg of 6.7% higher strength cannabis; estimated 3.8 mg THC inhaled) were associated with an analgesic and anti-spastic response [276] Many of the psychoactive effects showed a dose-dependency, with the low dose (2.9%) condition associated with lower intensity of psychoactive effects.

These above-mentioned studies suggest that, at least in the case of chronic neuropathic pain, *psychoactive effects can be separated from therapeutic effects* and that *very low doses* of THC may actually be sufficient to produce analgesia while keeping psychoactive effects to a minimum.

A review of U.S. state clinical trials on the use of smoked cannabis for the treatment of chemotherapy-induced nausea and vomiting (CINV) reported that plasma THC levels > 10 ng/mL were associated with the greatest suppression of nausea and vomiting but plasma levels between 5 and 10 ng/mL were also effective [296].

Table 3: 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 4: Comparison between Cannabis and Prescription Cannabinoid Medications

	Cannabinoid (Generic name)	Brand/Registered name	Principal constituents/ Source	Official status in Canada	Approved indications	Onset of effects (O) / Peak effects (P)/ Duration of action (D)	Route of administration	Availability on provincial/ territorial formulary
Rx cannabinoids	Dronabinol†	Marinol®†[227]	Synthetic Δ^9-THC	Approved (but no longer available in Canada— see note)†	AIDS-related anorexia associated with weight loss; Severe nausea and vomiting associated with cancer chemotherapy	O: 30 – 60 min P: 2 – 4 h D: Psychoactive effect: 4 – 6h Appetite stimulant effect : up to 24 h or longer	Oral	MB†; NB†; NS†; ON†; PE†; QC†; YT†
	Nabilone	Cesamet®[492] RAN-Nabilone TEVA-Nabilone CO-Nabilone PMS-Nabilone ACT-Nabilone	Synthetic Δ^9-THC analogue	Marketed	Severe nausea and vomiting associated with cancer chemotherapy	O: 60 – 90 min P: 3 – 4 h 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®[431]	Botanical extract from established and well-characterized *C. sativa* strains	Marketed *	*	O: 5 – 30 min P: 1.5 – 4 h D: 12 – 24 h	Oro-mucosal spray	NS
	Cannabidiol (CBD)	Epidiolex®	Botanical extract from established and well-characterized *C. sativa* strains	Being studied in clinical trials - Not an approved product (as of March 2018)	N/A	N/A	Oral	N/A
Plant product	Cannabis (smoked or vapourized)	N/A	*C. sativa (various)*	Not an approved product	N/A	O: 5 min P: 20 – 30 min D: 2 – 3 h [495, 594]	Smoking or inhalation	N/A
	Cannabis (oil for sublingual administration)	N/A	*C. sativa (various)*	Not an approved product	N/A	O: 5 – 30 min P: 1.5 – 4 h D: 12 – 24 h [based on Sativex®[431]]	Oral	N/A

	Cannabis (oral edible)	N/A	*C. sativa (various)*	Not an approved product	N/A	O: 30 – 90 min P: 2 – 3 h D: 4 – 12 h [400]	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.

AB: Alberta; BC: British Columbia; MB: Manitoba; N/A: not applicable; NB: New Brunswick; NL: Newfoundland and Labrador; NS: Nova Scotia; NU : Nunavut; NT: Northwest Territories; ON: Ontario; PE: Prince Edward Island; QC: Quebec; Rx: prescription; SK: Saskatchewan; YT: Yukon

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 of THC are estimated from the information in the monograph for Marinol® (dronabinol, no longer available in Canada). 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% [227]. 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% [407]. An 8 mg orally-administered THC tablet (Namisol®) yielded a mean plasma THC C_{max} of 4 ng/mL and a similar mean plasma 11-hydroxy-THC C_{max} [595]. Tea prepared from *Cannabis* flowering tops and leaves has been documented, but no data are available regarding efficacy [422].

Marinol

Although Marinol® (dronabinol) is no longer available for sale in Canada, the Marinol® 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 [227]. 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 CINV, a dosage of 5 mg t.i.d. or q.i.d. is suggested. In either case, the dose should be carefully titrated to avoid the manifestation of adverse effects. Please consult the Marinol® drug product monograph for more detailed instructions.

Cesamet

The Cesamet® (nabilone) product monograph suggests administration of 1 to 2 mg of the drug, twice a day, with the first dose given the night before administration of the chemotherapeutic medication [492]. A 2 mg dose of nabilone gave a mean plasma concentration of 10 ng/mL nabilone, 1 to 2 h after administration. The second dose is usually administered 1 to 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 PTSD [578, 596, 597]. Please consult the Cesamet® drug product monograph for more detailed instructions.

Epidiolex

Data from an open-label clinical study of Epidiolex® for treatment-resistant childhood-onset epilepsy suggest that dosing with Epidiolex® (98 – 99% pure CBD oil) begin at a starting dose of 2 to 5 mg/kg per day divided in twice-daily dosing in addition to baseline antiepileptic drug regimen, then up-titrated by 2 to 5 mg/kg once a week until intolerance or a maximum dose of 25 mg/kg per day is reached [262]. In some specific situations, the study authors mention that an increase to a maximum dose of 50 mg/kg per day could be considered. In patients with drug- resistant seizures in the Dravet syndrome [576] or treatment-resistant Lennox-Gastaut syndrome [577], a dose of 20 mg/kg per day is efficacious and generally well tolerated.

Cannabis oil

Data from an open-label longitudinal study of cannabis oil for patients with treatment-resistant chronic non-cancer pain reported that patients titrated their cannabis oil dose starting with one drop of cannabis oil per day, increasing in increments of one drop of oil per dose, three times per day, until satisfactory analgesia was achieved or until side effects appeared [582]. THC concentrations ranged from 11 – 19% and 0.5 – 5.5% CBD in cannabis oil in this study.

An open-label, pilot study of add-on oral THC (25 mg/ml in olive oil) for the treatment of symptoms associated with PTSD suggested dosing begin by placing 2.5 mg THC b.i.d. beneath the tongue (i.e. 0.1 mL of the oil solution) 1 h after waking up and 2 h before going to bed [571]. Maximum daily dose was 5 mg b.i.d. (i.e. 0.2 mL b.i.d.), or a total 10 mg daily dose (i.e. 0.4 mL).

3.3 Oro-mucosal

Dosing with nabiximols (Sativex®) is described in the product monograph along with a titration method for proper treatment initiation [431]. Briefly, dosing indications in the drug product monograph suggest that on the first day of treatment patients take one spray during the morning (anytime between waking and noon), and another in the afternoon/evening (anytime between 4 p.m. and bedtime). On subsequent days, the number of sprays can be increased by one spray per day, as needed and tolerated. A fifteen-minute time gap should be allowed between sprays. During the initial titration, sprays should be evenly spread out over the day. If at any time unacceptable adverse reactions such as dizziness or other CNS-type reactions develop, dosing should be suspended or reduced or the dosing schedule changed to increase the time intervals between doses. According to the drug product monograph, the average dose of nabiximols is five sprays per day (i.e. 13 mg Δ^9-THC and 12.5 mg CBD) for patients with MS, whereas those patients with cancer pain tend to use an average of eight sprays per day (i.e. 21.6 mg Δ^9-THC and 20 mg CBD). The majority of patients appear to require 12 sprays or less; dosage should be adjusted as needed and tolerated. Administration of four sprays to healthy volunteers (total 10.8 mg Δ^9-THC and 10 mg CBD) was associated with a mean maximum plasma concentration varying between 4.90 and 6.14 ng/mL Δ^9-THC and 2.50 to 3.02 ng/mL CBD depending whether the drug was administered under the tongue or inside the cheek. Please consult the Savitex® drug product monograph for more detailed information.

3.4 Vapourization

The Dutch Office of Medicinal Cannabis has published "rough" guidelines on the use of vapourizers [422]. Although the amount of cannabis used per day needs to be determined on an individual basis, the initial dosage should be low and may be increased slowly as symptoms indicate. The amount of cannabis to be placed in the vapourizer may vary depending on the type of vapourizer used.

Studies using the Volcano® vapourizer have reported using up to 1 g of dried cannabis in the chamber, but 50 to 500 mg of plant material is typically used [414]; Δ^9-THC concentrations up to 6.8% have been tested with the Volcano® vapourizer [402, 414]. Subjects appeared to self-titrate their intake in accordance with the Δ^9-THC content of the cannabis [402]. Peak plasma Δ^9-THC levels varied between 70 and 190 ng/mL depending on the strength of Δ^9-THC. The levels of cannabinoids released into the vapour phase increased with the temperature of vapourization [414]. Vapourization temperature has typically been reported to be between 180 – 195 °C [422]; higher temperatures (e.g. 230 °C) greatly increase the amounts of cannabinoids released, but also increase the amounts of by-products [414].

One study reported the use of a uniform "cued" puffing procedure for vapourization with the Volcano® vapourizer: inhalation for five seconds, holding the breath for 10 seconds, and a 45-second pause before a repeat inhalation [280]. Participants inhaled as much of the 900 mg dose of dried cannabis (3.56% THC; 32 mg THC) as they could tolerate. Vapourization temperature was set to 190 °C.

In another study, patients followed a similar "cued-puff" procedure and inhaled 4 puffs, followed by an additional round of between 4 and 8 puffs 2 h later for a total of between 8 and 12 puffs over a 2 h period [598].

Another vapourization study also with the Volcano®, using the same cued-puff procedure, used 400 mg of dried cannabis of three variable strengths (1%, 4% and 7% THC or 4, 16 and 28 mg THC per dosing session) [599]. Vapourization temperature was 200 °C.

Lastly, a more recent set of studies again using the Volcano® vapourizer and the same "cued-puff" procedure, reported using 400 mg of dried cannabis with either 2.9% (12 mg THC) or 6.7% THC (27 mg THC), with a vapourizing temperature of 185 °C [276]. Subjects inhaled 4 puffs at the beginning of the testing session, followed by an additional round of between 4 and 8 puffs 3 h later for a total of between 8 and 12 puffs over a 3 h period.

Data from a pilot clinical trial with the Syqe Inhaler™ has shown that an inhaled dose of as little as 3 mg THC (~1.5 mg THC absorbed, delivered from an amount as low as **15 mg** of dried cannabis plant material at a potency of 20% THC) was associated with analgesic efficacy with minimal adverse effects [58]. THC was detected in the plasma within 1 min following inhalation and reached a maximum within 3 min at a mean THC concentration of 38 ng/ml.

4.0 Potential Therapeutic Uses

While there are countless anecdotal reports concerning the therapeutic uses of cannabis, clinical studies supporting the safety and efficacy of cannabis for therapeutic purposes in a variety of disorders are limited, but slowly increasing in number. Furthermore, the current level of evidence for the safety and efficacy of cannabis for medical purposes does not meet the requirements of the *Food and Drugs Act* and its Regulations except for those products that have received a notice of compliance and market authorization from Health Canada. With the exception of one small open-label, pilot clinical study of orally-administered THC in an olive oil solution for symptoms associated with PTSD and clinical trials of orally-administered CBD in an oil solution (Epidiolex®) for symptoms associated with childhood epilepsy (see section **4.6 Epilepsy**), there are no well-controlled clinical studies on the use of other orally-administered cannabis products such as cannabis edibles (e.g. cookies, baked goods) or topicals for therapeutic purposes.

It has been repeatedly noted that the psychotropic side effects associated with the use of (psychoactive) cannabinoids have been found to limit their therapeutic utility [23, 55, 57, 268, 600]. **Table 5** ("Published Positive, Randomized, Double-Blind, Placebo-Controlled, Clinical Trials on Smoked/Vapourized Cannabis and Associated Therapeutic Benefits") summarizes the information on published clinical trials that have been carried out thus far using smoked/vapourized cannabis and oil-based products.

A comprehensive review of 72 controlled clinical studies evaluating the therapeutic effects of cannabinoids (mainly orally administered THC, nabilone, nabiximols, or an oral extract of cannabis) up to the year 2005 reported that cannabinoids present an interesting therapeutic potential as anti-emetics, appetite stimulants in debilitating diseases (cancer and AIDS), analgesics, and in the treatment of MS, SCIs, Tourette's syndrome (TS), epilepsy, and glaucoma [601].

However, a more recent systematic review and meta-analysis of randomized clinical trials of cannabinoids (i.e. smoked cannabis, nabiximols, nabilone, dronabinol, CBD, THC, levonontradol, ajulemic acid) reported that most trials showed improvement in symptoms associated with cannabinoid use but the associations did not reach statistical significance in all trials [179]. Compared with placebo, cannabinoids were associated with a greater average number of patients showing a complete improvement in nausea and vomiting, reduction in pain, a greater average reduction in numerical rating scale pain assessment, and average reduction in the Ashworth spasticity scale [179]. There was also an increased risk of short-term adverse events with cannabinoids. Commonly reported adverse events included dizziness, dry mouth, fatigue, somnolence, euphoria, vomiting, disorientation, drowsiness, confusion, loss of balance and hallucinations [179]. Overall, the review and meta-analysis conducted using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach suggested that there was moderate-quality evidence to support the use of cannabinoids for the treatment of chronic neuropathic or cancer pain as well as MS-associated spasticity, but low-quality evidence to support use for CINV, weight gain in HIV infection, sleep disorders, and TS [179]. The review and meta-analysis only included only one study with smoked cannabis and all other included clinical studies were with oral or oro-mucosal administration of cannabinoid-based medicines (e.g. nabiximols, nabilone, dronabinol).

The National Academy of Sciences, Engineering and Medicine (NASEM) has published a report on the health effects of cannabis and cannabinoids [602]. This comprehensive report includes information on the therapeutic effects of cannabis and the cannabinoids but also other health effects such as cancer, cardiometabolic risks, respiratory disease, immunity, injury and death, prenatal, perinatal and neonatal effects, psychosocial and mental health effects. It also discusses challenges and barriers in conducting cannabis research as well as recommendations to support and improve cannabis research. Much of the evidence included in the report came from systematic reviews and meta-analyses and selected high quality primary research. Evidence gathered from *in vitro* or *in vivo* animal studies was not included .

Dronabinol is the generic name for the oral form of synthetic Δ^9-THC and is marketed in the U.S. as Marinol®. It was available for sale in Canada in capsules containing 2.5, 5, or 10 mg of the drug dissolved in sesame oil. It is indicated for the treatment of severe CINV in cancer patients, and for AIDS-related anorexia associated with weight loss [227]. The drug is **no longer sold in Canada** (post-market discontinuation of the drug product as of February 2012; not for safety reasons). Please consult the Marinol® drug product monograph for more detailed information.

Nabilone is the generic name for an orally administered synthetic structural analogue of Δ^9-THC, which is marketed in Canada as Cesamet® but also now available in generic forms (e.g. RAN-nabilone, PMS-nabilone, TEVA-nabilone, CO-nabilone, ACT-nabilone). It is available as capsules (0.25, 0.5, 1 mg) and is indicated for severe CINV in cancer patients [492]. Please consult the Cesamet® drug product monograph for more detailed instructions.

Nabiximols is the generic name for a whole-plant extract of two different, but standardized, strains of *Cannabis sativa* giving an oro-mucosal spray product containing approximately equivalent amounts of Δ^9-THC (27 mg/mL) and CBD (25 mg/mL), and other cannabinoids, terpenoids, and flavonoids per 100 µl of dispensed spray. Nabiximols is marketed as Sativex® in Canada and has received a notice of compliance for use 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 and (with conditions) as an adjunctive analgesic in adult patients with advanced cancer who experience moderate to severe pain during the highest tolerated dose of strong opioid therapy for persistent background pain [431]. Please consult the Sativex® drug product monograph for more detailed instructions.

Epidiolex® is the brand name for a whole-plant cannabis extract of a high CBD strain of *Cannabis sativa* and is an oral oil-based solution product containing > 98% CBD at a concentration of 100 mg/ml. Epidiolex® has received Orphan Drug Designation in the U.S. for the treatment of Lennox-Gastaut Syndrome, Dravet Syndrome and Tuberous Sclerosis Complex. At the time of writing this document Epidiolex® has not received a Notice of Compliance from Health Canada and is not marketed in Canada.

The existing scientific and clinical evidence for cannabis and certain cannabinoids in treating various symptoms associated with various medical conditions is summarized in the following sections beginning on the next page.

Table 5: Published Positive, Randomized, Double-Blind, Placebo-Controlled, Clinical Trials on Smoked/Vapourized Cannabis and Associated Therapeutic Benefits

Primary medical conditions and associated secondary end-points (if any) for which benefits were observed	**Percent and dose of Δ^9-THC (if known)**	**Trial duration; and number of patients/participants**	**Reference**
HIV/AIDS-associated weight loss	One cannabis cigarette (~800 mg) containing 1.8% or 3.9% THC by weight, smoked once daily (i.e. one dose per day) (~14 – 31 mg Δ^9-THC /day)	8 sessions total (3 sessions per week); 30 participants	224
HIV/AIDS-associated weight loss; disease-associated mood and insomnia	One cannabis cigarette (~800 mg) containing 2.0% or 3.9% THC by weight, smoked four times per day (i.e. four doses per day) (~64 – 125 mg of Δ^9-THC /day)	4 days total; 10 participants	223
Multiple sclerosis-associated pain and spasticity	One cannabis cigarette (~800 mg) containing 4% THC by weight, smoked once per day (i.e. one dose per day) (~32 mg Δ^9-THC /day)	3 days total; 30 patients	278
Central and peripheral chronic neuropathic pain (various etiologies)	One cannabis cigarette (~800 mg) containing either 3.5% or 7% THC by weight, smoked in bouts over a 3 h period (i.e. one dose per day) (daily dose of THC unavailable)	1 day total; 38 patients	222
Chronic neuropathic pain from HIV-associated sensory neuropathy	One cannabis cigarette (~900 mg) containing 3.56% THC by weight, smoked three times daily (i.e. three doses per day) (~96 mg Δ^9-THC /day)	5 days total; 25 patients	195
HIV-associated chronic neuropathic pain refractory to other medications	One cannabis cigarette (~800 mg) containing between 1 and 8% THC by weight, smoked four times daily (i.e. four doses per day) (daily dose of THC unavailable)	5 days total; 28 patients	281
Chronic post-traumatic or post-surgical neuropathic pain refractory to other medications and associated insomnia	One 25 mg dose of cannabis containing 9.4% THC by weight, smoked three times daily (i.e. three doses per day) (~7 mg Δ^9-THC /day)	5 days total; 21 patients	59

Chronic pain of various etiologies (musculoskeletal, post-traumatic, arthritic, peripheral neuropathy, cancer, fibromyalgia, migraine, multiple sclerosis, sickle cell disease, thoracic outlet syndrome)	One 900 mg dose of vapourized cannabis containing 3.56% THC by weight administered three times per day (one dose the first day, three doses per day for next three days, one dose the last day) (~96 mg Δ^9-THC /day)	5 days total; 21 patients	280
Neuropathic pain of various etiologies (spinal cord injury, complex regional pain syndrome (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)	Inhalation of vapourized cannabis (800 mg) containing either a low (1.29% or 10.3 mg Δ^9-THC) or a medium-dose of Δ^9-THC (3.53% Δ^9-THC or 28.2 mg Δ^9-THC)	3 sessions total; 39 patients	598
Crohn's disease	One cannabis cigarette (500 mg) containing 23% THC by weight, smoked twice daily (i.e. two doses per day) (23 mg Δ^9-THC /day)	8 weeks; 21 patients	603
Neuropathic pain of various etiologies	Inhalation of a single vapourized dose of 15 mg dried containing 20% Δ^9-THC by weight (~3 mg Δ^9-THC)	One session only; 10 patients	58
Diabetic peripheral neuropathy (i.e. diabetes mellitus type I and II)	Inhalation of single vapourized doses of dried cannabis (400 mg/dose) containing either low (1% Δ^9-THC or 4 mg Δ^9-THC), medium (4% Δ^9-THC or 16 mg Δ^9-THC) or high (7% Δ^9-THC or 28 mg Δ^9-THC) doses of Δ^9-THC (four single dosing sessions; each separated by two weeks)	4 sessions total; 16 patients	599
Neuropathic pain from spinal cord injury or disease	Inhalation of between 8 and 12 puffs from 400 mg of dried cannabis (2.9% and 6.7% THC)	3 sessions total; 42 patients	276

4.1 Palliative care

- ***The evidence thus far from some observational studies and clinical studies suggests that cannabis (limited evidence) and prescription cannabinoids (e.g. dronabinol, nabilone, or nabiximols) may be useful in alleviating a wide variety of single or co-occurring symptoms often encountered in the palliative care setting.***
- ***These symptoms may include, but are not limited to, intractable nausea and vomiting associated with chemotherapy or radiotherapy, anorexia/cachexia, severe intractable pain, severe depressed mood and anxiety, and insomnia.***
- ***A limited number of observational studies suggest that the use of cannabinoids for palliative care may also potentially be associated with a decrease in the number of some medications used by this patient population.***

Among the goals of palliative care described by the WHO are relief from pain and other distressing symptoms, and the enhancement of quality of life (QoL) [604]. While integration of cannabis into mainstream medical use can be characterized as extremely cautious, its use appears to be gaining some ground in palliative care settings where the focus is on individual choice, patient autonomy, empowerment, comfort and especially QoL [605]. Nevertheless, establishing the effectiveness of cannabis as a viable treatment option in a palliative care context requires a careful assessment of its effects in a wide range of conditions; such evidence is not yet abundant and further research is needed [606]. Certain patient populations (e.g. the elderly or those suffering from pre-existing psychiatric disease) may also be more sensitive or susceptible to experiencing adverse psychotropic, cognitive, psychiatric or other effects [607, 608].

Data from observational studies
A prospective, non-randomized, and unblinded observational case-series study assessing the effectiveness of adjuvant nabilone therapy in managing pain and symptoms experienced by 112 advanced cancer patients in a palliative care setting reported that those patients using nabilone had a lower rate of starting NSAIDs, tricyclic anti-depressants, gabapentin, dexamethasone, metoclopramide, and ondansetron and a greater tendency to discontinue these drugs [288]. Patients were prescribed nabilone for pain relief (51%), for nausea (26%), and for anorexia (23%). Treated patients were started on 0.5 or 1 mg nabilone at bedtime during the first week and titrated upwards in increments of 0.5 or 1 mg thereafter. At follow-up, the majority of patients were on a 2 mg daily nabilone dose with a mean daily dose of 1.79 mg. The two primary outcomes of the study, pain and opioid use in the form of total morphine sulfate equivalents were reduced significantly in treated patients compared to untreated patients. Side effects from nabilone consisted mainly of dizziness, confusion, drowsiness, and dry mouth. Patients also demonstrated less tendency to initiate additional new medications and could reduce or discontinue baseline medications.

One observational study that examined over 100 self-reported cannabis-using patients in a cancer palliative care setting reported significant improvement in a variety of cancer and anti-cancer treatment-related symptoms including nausea, vomiting, mood disorders, fatigue, weight loss, anorexia, constipation, sexual function, sleep disorders, itching, and pain [609]. While the daily dose of cannabis remained constant throughout the study period, 43% of patients using pain medications reported a dose reduction and 1.7% reported a dose increase. In addition, 33% of cannabis-using patients reduced the dose of their anti-depression/anti-anxiety medications. No significant adverse effects were noted in those using cannabis, with the exception of a reported reduction in memory in about 20% to 40% of the study sample. The reported decrease in memory among a proportion of the study sample could be a function of cannabis use along with the use of other medications such as opioids, anti-depressants, or even vary with age. Improvements in symptom and distress scores were also noted. Limitations of the study included its observational nature, the lack of an appropriate control group, and the reliance on self-report.

Another observational study looking at the patterns of cannabis use among adult Israeli advanced cancer patients reported that of approximately 17,000 cancer patients monitored at a single Israeli healthcare institution, 279 patients were authorized to use cannabis for medical purposes; among these, the median age of patients was 60 years (range: 19 – 93 years) and the most common cancer diagnoses were lung (18%), ovarian (12%), breast (10%), colon (9%), and pancreatic (7.5%), and the majority (84%) of the patients had metastatic disease [237]. The majority of patients (71%) were designated as active palliative, supportive (13%), and curative (6%). In most patients, cannabis was requested for multiple indications. The most common indication for which cannabis was prescribed was pain (76%), with anorexia (56%), generalized weakness (52%), and nausea (41%) also being common indications. Furthermore, 70% of patients reported improvement in pain control and general well-being, 60% reported improvement in appetite, 50% reported reduced nausea and vomiting, and 44% reported reduced anxiety with cannabis. Eighty-three percent of patients rated the overall efficacy of cannabis as being high. The most common route of administration (more than 90%) was smoking. While the majority of responders (62%) reported no adverse effects associated with the use of cannabis, the most commonly reported adverse effects were fatigue (20.3%) and dizziness (18.8%), while a minority of patients reported delusions (6%) and mood change (4.4%).

For information on the use of cannabis/cannabinoids for the **control of nausea and vomiting** please consult **Section 4.3** of this document. For additional information on the use of cannabis/cannabinoids for **anorexia/cachexia associated with HIV/AIDS infection or cancer,** please consult **Sections 4.4.1 and 4.4.2**, respectively. For further information on the use of cannabis/cannabinoids for **chronic pain syndromes** (including cancer pain), please consult **Sections 4.7.2.2 and 4.7.2.3**. For further information on the use of cannabis/cannabinoids in the treatment of **sleep disorders associated with chronic diseases** please see **Section 4.9.5.2**, and please consult **Section 4.9.9** for information on the use of cannabis/cannabinoids in **oncology**.

4.2 Quality of life

- ***The available clinical studies report mixed effects of cannabis and prescription cannabinoids on measures of quality of life (QoL) for a variety of different disorders.***

A handful of clinical studies have used standardized QoL instruments to measure whether the use of cannabis or prescription cannabinoids (e.g. nabilone, dronabinol, or nabiximols) is associated with improvements in QoL. The evidence from these studies is summarized below.

Clinical studies with dronabinol

A randomized, double-blind, placebo-controlled, crossover trial of dronabinol (maximum dose of 10 mg Δ^9-THC per day, for a total of three weeks) for the treatment of central neuropathic pain in patients suffering from MS reported statistically significant improvements in measures of QoL (36-Item Short Form Health Survey, SF-36; measures for bodily pain and mental health) [610].

A two-centre, phase II, randomized, double-blind, placebo-controlled 22-day pilot study carried out in adult patients suffering from chemosensory alterations (i.e. changes in olfaction and gustation) and poor appetite associated with advanced cancer of various etiologies reported improved and enhanced chemosensory perception among patients treated with dronabinol (2.5 mg b.i.d.) compared to those receiving placebo [611]. The majority (73%) of dronabinol-treated patients self-reported an increased overall appreciation of food compared to those receiving placebo (30%). While global scores on the Functional Assessment of Anorexia-Cachexia Therapy (FAACT) QoL instrument improved to a similar extent for dronabinol and placebo-treated groups, the FAACT sub-domain for anorexia-cachexia-related nutritional well-being improved with dronabinol compared to placebo. Statistically significant improvements were also noted for quality of sleep and relaxation with dronabinol treatment compared to placebo. According to the study authors, negative psychoactive effects were minimized by starting patients at a low dose (2.5 mg once a day for three days) followed by gradual dose escalation (up to a maximum of 7.5 mg dronabinol per day).

Clinical studies with cannabis extract

A multi-centre, phase III, randomized, double-blind, placebo-controlled, three-arm, parallel study in adult patients with advanced incurable cancer and suffering from cancer-related anorexia-cachexia syndrome concluded that neither cannabis extract (2.5 mg Δ^9-THC, 1 mg CBD, for six weeks) nor THC (2.5 mg Δ^9-THC b.i.d., for six weeks) provided any statistically significant benefit compared to placebo on measures of QoL (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, Core Module – EORTC QLQ-C30) [315].

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 (VAS for pain, and the Fibromyalgia Impact Questionnaire) [596].

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 EuroQoL five dimensions questionnaire, EQ-5D, Index Score) and overall patient status compared to placebo [612]. Doses of nabilone ranged from 1 to 4 mg/day; treatment duration was five weeks.

A seven-week, randomized, placebo-controlled study comparing the effects of nabilone to placebo on QoL and side effects during radiotherapy for head and neck carcinomas reported that at the dosage used (0.5 – 2.0 mg/day titrated upwards over study duration), nabilone did not lengthen the time necessary for a 15% deterioration of QoL (measured on the EORTC QLQ-C30 and the EORTC QLQ-Head and Neck Module, H&N35, scales), and it was not better than placebo for relieving pain and nausea, or improving loss of appetite and weight, mood and sleep [613]. There was also no statistically significant difference in the occurrence of adverse effects between the nabilone and placebo groups.

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) [614].
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) [615].

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 [284]. 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).

Clinical and observational 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 QoL instrument) [59].

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 QoL questionnaire in patients who used cannabis compared to non-users [184]. 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.

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' QoL, caused a statistically significant increase in subjects' weight, and improved the clinical disease activity index in patients with Crohn's disease [279]. 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. Patients also reported a statistically significant reduction in physical pain as well as improvement in mental distress.

A recent systematic review and meta-analysis of 20 studies [11 randomized controlled trials (RCTs); 9 cohort/cross-sectional designs) examining the impact of a variety of cannabinoid-based products (herbal cannabis, nabiximols, nabilone, dronabinol, dexanabinol] on health-related quality of life (HRQoL) across multiple conditions reported no overall significant associations. The authors attributed the null findings to the heterogeneity of study characteristics, and the limitation in which HRQoL were secondary and not primary outcomes in most studies. However, the studies showing a positive relationship between cannabinoids and HRQoL were more likely to be from pain-related symptoms (neuropathic pain, multiple sclerosis, headaches, inflammatory bowel disease), while negative relationships were observed mostly in HIV patients who reported significant reductions in physical and mental HRQoL [616].

4.3 Chemotherapy-induced nausea and vomiting

- ***Pre-clinical studies show that certain cannabinoids (THC, CBD, THCV, CBDV) and cannabinoid acids (THCA and CBDA) suppress acute nausea and vomiting as well as anticipatory nausea.***
- ***Clinical studies suggest that certain cannabinoids and cannabis (limited evidence) use may provide relief from chemotherapy-induced nausea and vomiting (CINV).***

CINV is one of the most distressing and common adverse events associated with cancer treatment [617]. In the absence of effective anti-emetics, chemotherapy-associated nausea can be so severe that as many as 20% of patients opt to discontinue chemotherapeutic treatment [618]. Once a patient experiences nausea, it tends to persist throughout treatment and make subsequent episodes of nausea more severe [619]. Post-treatment nausea is also associated with impaired patient functioning, increased anxiety, depression, and reduced QoL which can all negatively impact treatment adherence or even cause discontinuation of treatment entirely [620].

While nausea typically occurs before vomiting, the two have distinct neural circuitries and can be separated behaviourally [295]. Furthermore, while the central mechanisms of vomiting are well-known, those responsible for nausea remain less well understood [295]. Nevertheless, scientific studies point to the insular cortex as the seat of sensations such as nausea and disgust, with other central regions (e.g. area postrema, parabrachial nucleus) as well as GI input also contributing to the generation of nausea [295, 621].

Whereas chemotherapy-induced vomiting generally appears to be well-controlled with current first-line therapies/triple-combination therapies (e.g. 5-HT_3 antagonists, neurokinin-1 antagonists, and corticosteroids), the associated acute, delayed, and especially anticipatory nausea remain more poorly controlled and the use of cannabis/cannabinoids may provide some measure of benefit in such cases [109, 297, 620]. A significant proportion (25 – 59%) of patients undergoing chemotherapy experience anticipatory nausea during treatment and once it develops, it is refractory to standard treatment with 5-HT_3 antagonists [620]. Non-specific anti-anxiety treatments (e.g. benzodiazepines) are used to treat anticipatory nausea but drawbacks include significant sedation [620].

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 ECS in the regulation of nausea and vomiting [109, 295, 620, 622-628]. CB_1 and CB_2 receptors have been found in areas of the brainstem associated with emetogenic control [629, 630], and results from animal studies suggest the anti-nausea and anti-emetic properties of certain cannabinoids (e.g. Δ^9-THC, dronabinol, nabilone) are most likely related to their agonistic actions at centrally-located CB_1 receptors [99, 109, 631]. Levels of 2-AG are increased in the visceral insular cortex during an acute episode of nausea in rats and localized blockade of 2-AG through targeted MAGL inhibition in the insular cortex reduces acute nausea [294]. Similarly, infusion of 2-AG into the insular cortex dose-dependently blocks anticipatory nausea, while infusion of anandamide was without effect [632]. These findings suggest that 2-AG, but not anandamide, drives acute and anticipatory nausea. Elsewhere, elevation of endocannabinoids such as anandamide and 2-AG by inhibition of the endocannabinoid degradative enzymes FAAH and MAGL, has been shown to suppress acute and anticipatory nausea in animal models [295, 633] and localized infusion of a peripherally-restricted CB_1 receptor agonist into the visceral insular cortex suppressed nausea-like behaviour in rats, whereas systemic administration had no effect [621].

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 [99, 100]. 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 [634], a target of current standard anti-emetic drugs, raising the possibility that cannabinoids may exert their anti-emetic action through more than one mechanism. Other studies carried out in animal models of nausea and vomiting have shown that CBD (5 mg/kg, subcutaneous (s.c.)) suppressed chemical-induced vomiting (and nausea) through potential activation of somatodendritic 5-HT_{1A} autoreceptors located in the dorsal raphe nucleus [627], while another study showed that the anti-nausea/vomiting effects of CBD could be reversed by pre-treatment with CBG (5 mg/kg, i.p.) [628].

Cannabinoid acids and other cannabinoids

Additional work has revealed novel and important roles for cannabinoid acids (i.e. THCA, CBDA) in suppressing nausea and vomiting in animal models [116, 117, 622, 623, 625]. In one study, when administered alone, a very low dose (0.5 µg/kg i.p.) of CBDA suppressed behaviour modelling acute nausea, and a subthreshold dose of CBDA (0.1 µg/kg i.p.), when administered along with ondansetron at a dose of 1 µg/kg produced an enhancement of the acute anti-nausea effect [625]. In addition, the effective dose of CBDA that attenuated acute nausea was approximately 1 000 times lower than the effective dose for CBD [625]. THCA at doses of 0.5 and 0.05 mg/kg (i.p.) reduced behaviours modelling acute nausea and vomiting, and at a dose of 0.05 mg/kg (i.p.) reduced behaviours modelling anticipatory nausea in animal models of acute and anticipatory nausea, and vomiting [623].

THCA has been shown to lack CB_1 receptor activity [635] and administration of THCA was not associated with some of the classical animal behavioural signs of CB_1 receptor agonists (i.e. hypothermia, catalepsy) [623], supporting previous findings of lack of THCA-associated psychoactivity in animals [636]. THCA was also found to be at least 10 times more potent than THC in reducing acute and anticipatory nausea models [623].

Other work has shown that THC, CBDA, and the benzodiazepine chlordiazepoxide reduced behaviour modelling anticipatory nausea [622]. In this study, CBDA (0.001, 0.01, and 0.1 mg/kg i.p.) was shown to be between 5 and 500 times more potent than THC (0.5 mg/kg) in reducing anticipatory nausea and 20 times more potent than chlordiazepoxide (10 mg/kg). Treatment with CBDA was not associated with any effects on locomotor activity at any tested dose whereas chlordiazepoxide significantly reduced locomotor activity. Co-administration of subthreshold doses of CBDA (0.1 µg/kg i.p.) and THCA (5 µg/kg i.p.) reduced behaviour modelling anticipatory nausea, and pharmacological studies suggest the involvement of CB_1 (for THCA) and 5-HT_{1A} (for CBDA) receptors in the mechanism of suppression of anticipatory nausea. Further research is needed to resolve the conflicting evidence around the mechanism of action, if any, of THCA at the CB_1 receptor. As for CBDA, a dose as low as 1 µg/kg (i.p.) potently suppressed anticipatory nausea in an animal model and compared to the doses of CBD needed for the same degree of effect (1 – 5 mg/kg i.p.), CBDA could be said to be between 1 000 and 5 000 times more potent than CBD in suppressing anticipatory nausea.

Additional animal studies have shown that administration of subthreshold doses of THC (0.01 and 0.1 mg/kg i.p.) and CBDA (0.01 and 0.1 µg/kg i.p.) reduced acute nausea, and higher doses of THC (1.0 and 10 mg/kg i.p.) or CBDA (1.0 and 10 µg/kg i.p.) alone also reduced acute nausea [116]. In contrast to the effect seen for acute nausea, combined subthreshold doses of THC and CBDA did not suppress anticipatory nausea in animals [116]. Higher doses of either THC (1.0 and 10 mg/kg i.p.) and/or CBDA (1.0 and 10 µg/kg i.p.) were effective in reducing anticipatory nausea. The higher dose of THC (10 mg/kg) was associated with hypoactivity, and this was not attenuated by CBDA.

A subsequent study examined the effects of combining CBD and THC, and CBDA and THC on acute nausea and vomiting [117]. The study showed that 2.5 mg/kg CBD (i.p.), when combined with 1 mg/kg THC (i.p.), resulted in significant suppression of acute nausea and vomiting in an animal model and similarly, when 0.05 mg/kg (i.p.) CBDA was combined with 1 mg/kg THC, acute nausea and vomiting were significantly suppressed. Singular administration of either 2.5 mg/kg CBD, 1 mg/kg THC, or 0.05 mg/kg (i.p.) CBDA was not associated with any suppression of acute nausea and vomiting.

In addition to THC, CBD, THCA and CBDA, two other phytocannabinoids THCV and cannabidivarin (CBDV) have been studied, though to a far lesser extent, for their potential to alleviate nausea in animal models [620]. THCV at a dose of 10 mg/kg (i.p.) and CBDV at a dose of 200 mg/kg (i.p.) have been shown to reduce acute nausea in rats, potentially through a CB_1 receptor-independent mechanism, but nothing is known about their ability to suppress anticipatory nausea [626].

Taken together, the findings from the above pre-clinical studies suggest that Δ^9-THC, CBD, CBDA, and THCA can all suppress acute nausea and vomiting as well as anticipatory nausea to varying degrees, and with varying potencies and efficacies, whereas THCV and CBDV suppress acute nausea. Furthermore, certain subthreshold combinations of some of these cannabinoids can produce synergistic anti-nausea and vomiting effects compared to when used alone.

Clinical studies

The evidence for smoked cannabis and prescription cannabinoids such as nabilone (Cesamet®), dronabinol (Marinol®), (and levonantradol) in treating CINV has been reviewed [179, 210, 601, 637]. One systematic review and meta-analysis of 28 randomized controlled trials (RCTs) (N = 2 454 participants) of cannabinoids using the GRADE approach reported a greater benefit of cannabinoids compared with both active comparators and placebo, but statistical significance was not reached in all of the studies [179]. The average number of patients showing a complete anti-nausea and vomiting response was greater with prescription cannabinoids (dronabinol or nabiximols) than placebo (OR = 3.82 [95% CI 1.55 – 9.42]).

While prescription 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 [210, 637]. In some cases, patients appeared to prefer the cannabinoids to 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 [296]. Patients who smoked cannabis showed a 70 to 100% relief from nausea and vomiting, while those who used a Δ^9-THC capsule experienced 76 to 88% relief. 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. In all cases, patients were admitted only after they failed treatment with standard phenothiazine anti-emetics.

In one small open label trial with eight children with various blood cancers were administered Δ^8-THC (18 mg/m^2) two hours before the initiation of chemotherapy as well as every six hours for the next 24 hours showed that Δ^8-THC successfully prevented vomiting and no delayed nausea or vomiting episodes were observed in the next two days following antineoplastic treatment [100]. Δ^8-THC could also be administered at doses considerably higher than the doses of Δ^9-THC generally administered to adult patients, with a lack of major side effects.

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 [617, 637]. 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% CBN; 0.05% CBD) 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 [297]. Furthermore, only cannabis produced changes in mood and subjective state. In another 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 [638]. 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 [639, 640]. More research is required to determine if combination therapy provides added benefits above those observed with newer standard treatments.

A retrospective chart review of dronabinol use for CINV in an adolescent oncology population (i.e. leukemia, lymphoma, sarcoma, brain tumour) in a tertiary pediatric hospital reported that the majority of patients who received moderate or highly emetogenic chemotherapy and standard anti-emetogenic therapy (i.e. 5-HT_3 receptor antagonist and corticosteroids) also received dronabinol [641]. The most commonly prescribed dose of dronabinol in this study was 2.5 mg/m^2 oral solution every 6 h (as needed), and the median number of dronabinol doses received per hospitalization was 3.5. Sixty percent of the pediatric patients in this study were reported to have had a "good" response to dronabinol. Limitations of this study include retrospective design, lack of a comparison group, lack of chemotherapy standardization, and lack of standardized anti-emetic regimens.

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 [417, 642-646]. Nabilone (Cesamet®) and dronabinol (Marinol®) are indicated for the management of severe nausea and vomiting associated with cancer chemotherapy [227, 492], however dronabinol is no longer available for sale on the Canadian market. 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 [311, 647].

4.4 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 available evidence from human clinical studies suggests that cannabis (limited evidence) and dronabinol may increase appetite and caloric intake, and promote weight gain in patients with HIV/AIDS.***
- ***However the evidence for dronabinol is mixed and effects modest for patients with cancer and weak for patients with anorexia nervosa.***

The ability of acute cannabis exposure to increase appetite has been recognized anecdotally for many years [312]. In addition, results from epidemiological studies suggest that people actively using cannabis have higher intakes of energy and nutrients than non-users [648]. Controlled laboratory studies with healthy subjects suggest acute 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 [312, 313]. 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 [649-651]. Furthermore, increasing evidence suggests a role for the ECS 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 [19, 650-652]).

4.4.1 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.

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 [653]. The lack of an observed clinical effect in this study could have been caused by too low a dose of dronabinol.

Despite the findings of the above-noted study, AIDS-related anorexia associated with weight loss was an approved indication in Canada for dronabinol (Marinol®) (no longer available in Canada). 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) [654]. 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. 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. The use of higher doses of dronabinol (20 mg – 40 mg per day) has been reported both in the Marinol® product monograph [227] as well as in the literature [223, 224]. However, caution should be exercised in escalating dosage because of the increased frequency of dose-related adverse effects.

A clinical study that used higher doses of dronabinol or smoked cannabis showed that acute administration of high doses of 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, over a total of eight study sessions) increased caloric intake in experienced HIV-positive cannabis smokers with clinically significant muscle mass loss [224]. Another subsequent inpatient study employed even higher doses of dronabinol (20 – 40 mg total Δ^9-THC daily, for four days) and smoked cannabis (~800 mg cannabis cigarettes containing 2.0 and 3.0% THC, administered four times per day, with an estimated 64 – 125 mg total Δ^9-THC daily *in the cigarette*, over a total study period of four days) [223]. Both drugs produced substantial and comparable increases in food intake and body weight, as well as improvements in mood and sleep [223, 224]. Others have shown that the cannabis-associated increase in body weight in this patient population appears to result from an increase in body fat rather than lean muscle mass [655, 656].

A double-blind, cross-over, placebo-controlled pilot sub-study examining the effects of cannabis use on appetite hormones in HIV-infected adult men with HIV sensory neuropathy on combination anti-retroviral therapy (ART) found that compared to placebo, smoked cannabis (1 – 8% THC) was associated with significant increases in plasma levels of ghrelin (increase of 42% vs. decrease of 12% with placebo) and leptin (increase of 67% vs. 11.7% with placebo), and decreases in plasma levels of peptide YY (decrease of 14.2% vs. 23% increase with placebo) [657]. Higher THC levels were associated with greater increases in ghrelin showing a dose-response relationship, whereas higher THC levels were associated with smaller increases in leptin; no dose-response was observed for peptide YY.

A systematic review and meta-analysis of 28 RCTs (N = 2 454 participants) of cannabinoids (i.e. smoked cannabis, nabiximols, nabilone, dronabinol, CBD, THC, levonontradol, ajulemic acid) using the GRADE approach reported that there was some evidence that dronabinol was associated with an increase in weight when compared with placebo and that it may also be associated with increased appetite, greater percentage of body fat, reduced nausea, and improved functional status in patients with HIV/AIDS [179].

4.4.2 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 [658, 659]. 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 clinical trials with oral Δ^9-THC (dronabinol) or oral cannabis extract are mixed and the effects, if any, appear to be modest (reviewed in [314].

In two early studies, oral THC (dronabinol) improved appetite and food intake in some patients undergoing cancer chemotherapy [319, 320]. 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 [317, 318]. 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 [321]. 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) [315]. Furthermore, when compared to megestrol acetate, an orexigenic medication, dronabinol was significantly less efficacious in reported appetite improvement and weight gain [316].

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 [611]. 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).

According to a 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 [660]. Cancer cachexia is not an approved indication for dronabinol in either Canada or the U.S.

4.4.3 Anorexia nervosa

The ECS has been implicated in appetite regulation and is suspected to play a role in eating disorders such as anorexia nervosa [650, 661]. Increased peripheral ECS activity (i.e. increased plasma anandamide and increased CB_1 mRNA expression in blood) has been found in patients with eating disorders [662]. In spite of epidemiological and familial studies, which suggest a genetic basis for anorexia nervosa, genetic studies have thus far failed to agree on an association between genes coding for ECS proteins and the manifestation of anorexia nervosa [663, 664].

No studies have examined the effects of smoking cannabis on anorexia nervosa and limited information exists on the use of cannabinoids to treat anorexia nervosa. Furthermore, inter- and intra-species differences in animals with respect to anorexia nervosa-like behaviour have to some extent hampered pre-clinical research on the effects of Δ^9-THC in this disorder.

One study in a mouse model of anorexia nervosa reported conflicting results [665], 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 i.p.) [666].

A small, randomized, crossover trial of oral Δ^9-THC in female anorexic patients suggested that THC produced a weight gain equivalent to the active placebo (diazepam) [323]. 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.

Lastly, a four-week, prospective, double-blind, randomized, cross-over clinical study of 5 mg daily doses of dronabinol in 24 adult women with severe, chronic anorexia nervosa reported a small, yet significant increase in body mass index (BMI) compared to placebo [322].

4.5 Multiple sclerosis, amyotrophic lateral sclerosis, spinal cord injury and disease

- ***Evidence from pre-clinical studies suggests THC, CBD and nabiximols improve multiple sclerosis (MS) associated symptoms of tremor, spasticity and inflammation.***
- ***The available evidence from clinical studies suggests cannabis (limited evidence) and certain cannabinoids (dronabinol, nabiximols, THC/CBD) are associated with some measure of improvement in symptoms encountered in MS and spinal cord injury (SCI) including spasticity, spasms, pain, sleep and symptoms of bladder dysfunction.***
- ***Very limited evidence from pre-clinical studies suggests that certain cannabinoids modestly delay disease progression and prolong survival in animal models of amyotrophic lateral sclerosis (ALS), while the results from a very limited number of clinical studies are mixed.***

MS is an (auto)immune-mediated, demyelinating and neurodegenerative chronic disease of the CNS that affects between 2 and 3 million people worldwide and is characterized by periods of relapsing and remitting neurological attacks and accumulating disability over many years [667, 668]. Demyelination and axonal and neuronal loss within different neural pathways of the CNS lead to a variety of different cognitive, sensory and motor problems (e.g. pain and spasticity) that accumulate as the disease progresses [667]. ALS is a progressive neurodegenerative disease caused by the selective damage of motor neurons in the spinal cord, brainstem, and motor cortex [669]. Although most cases are sporadic, familial cases can occur in an autosomal recessive or dominant or dominant X-linked inheritance pattern [670]. The pathogenesis of ALS includes excitotoxic damage, chronic inflammation, oxidative stress, and protein aggregation [669].

One systematic review of the efficacy and safety of cannabinoids for the treatment of selected neurological disorders, including symptoms such as spasticity, central pain and painful spasms, urinary dysfunction, and tremor associated with, for example, MS suggested that, based on existing clinical trial data, cannabinoids were probably effective for reducing patient-reported and objective measures of spasticity, effective or probably effective for reducing central pain or painful spasms, probably effective for reducing the number of bladder voids/day, but probably ineffective for reducing bladder complaints and probably or possibly ineffective for reducing tremor [671].

In contrast to the findings of the above systematic review, a more recent systematic review and meta-analysis of 28 RCTs (N = 2 454 participants) of cannabinoids (i.e. smoked cannabis, nabiximols, nabilone, dronabinol, CBD, THC, levonontradol, ajulemic acid) using the GRADE approach reported that cannabinoids were associated with improvements in spasticity but that this failed to reach statistical significance [179]. Cannabinoids (nabiximols, dronabinol, and THC/CBD) were associated with a greater average improvement on the Ashworth scale for spasticity compared with placebo, although this did not reach statistical significance. Cannabinoids (nabilone and nabiximols) were also associated with a greater average improvement in spasticity assessed using numerical rating scales. The average number of patients who reported an improvement on a global impression of change score was also greater with nabiximols than placebo.

Differences between the findings from these two systematic reviews of cannabinoids for selected neurological disorders include differences in methodology, approach, and inclusion/exclusion criteria. Nevertheless, both systematic reviews suggest that cannabis/cannabinoids are associated with some measure of improvement in spasticity, spasms and pain in selected neurological disorders (e.g. MS, SCI/disease).

Below is a summary of the peer-reviewed evidence on the use of cannabis and cannabinoids in MS, ALS and SCI and disease.

4.5.1 Multiple sclerosis

A number of studies, both in patients suffering from MS and in animal models of the disease, suggest the disorder is associated with changes in endocannabinoid levels, although the findings are conflicting [667, 668, 672-675].

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 [667, 668, 676]). Lyman was one of the first to report the effects of Δ^9-THC in one such model [677]. 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. The treated animals also typically had a marked reduction in CNS tissue inflammation compared to untreated animals. Subsequent studies in murine models of MS have supported and extended these findings demonstrating that Δ^9-THC, but not CBD, ameliorated both tremor and spasticity and reduced the overall clinical severity of the disease [672, 678]. Further work highlighted the importance of the CB_1 receptor in controlling tremor, spasticity, and the neuro-inflammatory response. In contrast to findings with the CB_1 receptor, the exact function of the CB_2 receptor in MS remains somewhat unclear, although it is believed to play a role in regulating the neuro-inflammatory response [678-680].

Two studies examined the potential therapeutic effects of three kinds of botanical-derived cannabis extracts on different mouse models of MS (i.e. Theiler's murine encephalomyelitis virus-induced demyelinating disease and the experimental autoimmune encephalitis) [681, 682]. Extracts used were a nabiximols-like extract, containing a 1:1 ratio of THC : CBD at 10 mg/kg for each phytocannabinoid, a THC-rich extract (5 mg/kg or 20 mg/kg) containing 67.1% THC, 0.3% CBD, 0.9% CBG, 0.9% CBC, and 1.9% other phytocannabinoids, or a CBD-rich extract (5 mg/kg or 20 mg/kg) containing 64.8% CBD, 2.3% THC, 1.1% CBG, 3.0% CBC, and 1.5% other phytocannabinoids. One of the studies reported that a 10-day treatment regimen with the nabiximols-like extract improved motor activity, reduced CNS infiltrates, microglial activity, axonal damage and restored myelin morphology and that the CBD-rich extract (5 mg/kg) alone appeared to alleviate the motor degeneration to a similar extent as the nabiximols-like extract, whereas the THC-rich extract (5 mg/kg) appeared to produce weaker effects [681]. The other study reported that treatment with the nabiximols-like extract (10 mg/kg) as well as the THC-rich extract (20 mg/kg), but not the CBD-rich extract (20 mg/kg), improved the neurological deficits typically observed with experimental autoimmune encephalitis in mice, as well as reduced the number and extent of cell aggregates present in the spinal cord; by contrast the CBD-rich extract appeared to only delay the onset of the disease without improving disease progression and reduced the cell infiltrates in the spinal cord [682]. Taken together, the studies suggest that optimal therapeutic effects in these animal models of MS depend on a combination of THC, CBD and potentially other phytocannabinoids. Another study reported that daily topical treatment with a 1% CBD cream exerted neuroprotective effects against the experimental autoimmune encephalomyelitis model of MS [445]. Treatment was associated with a diminished clinical disease score, attenuated paralysis of hind limbs, and improvements in histological scores (i.e. reduced demyelination, axonal loss, reduced inflammatory cell infiltration) and expression of pro-inflammatory cytokines.

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 [683]. 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 [684]. 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 [226]. 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 [225]. MS patients reported using cannabis to manage symptoms such as spasticity and chronic pain as well as anxiety and/or depression [225, 226]. MS patients taking cannabis 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 [225].

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 **CA**nnabis in **M**ultiple **S**clerosis (**CAMS**) study researching the effect of cannabinoids for the treatment of spasticity and other symptoms related to MS enrolled over 600 patients [387]. 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 (objective) 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®) [685]. Cannador® is not available in Canada at this time.

Other randomized clinical trials using standardized cannabis extract capsules (containing 2.5 mg Δ^9-THC and 0.9 mg CBD per capsule) [686] or nabiximols (Sativex®) [432, 687, 688] 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 [689] and is affected by patient symptoms, physical functioning, and psychological disposition [685]. Spasticity is also inherently difficult to measure, and has no single defining feature [688]. In addition, the reliability and sensitivity of the Ashworth scale (for objectively measuring spasticity) has been called into question [387, 688].

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 clinical trial in patients with clinically stable MS-associated spasticity and an Ashworth score greater than 2 [686]. 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. 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.

Nabiximols

A six-week, multi-centre, randomized, double-blind, placebo-controlled, parallel-group clinical 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 [432]. 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 non-medically or for medical purposes. While the global primary symptom score, 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, and in quality of sleep, but not in spasm frequency, pain, tremor, or bladder problems among other outcome measures. 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.

A long-term, open-label, follow-up clinical study of nabiximols (Sativex®) concluded that the beneficial effect observed in the study by Wade et al. 2004 [432] was maintained in patients who had initially benefited from the drug [687]. 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. Long-term use of nabiximols in this patient population was associated with reductions in *subjective* measures of spasticity, spasm frequency, pain, and bladder problems. 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.

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 [688]. Patients had to have significant spasticity in at least two muscle groups, and an Ashworth score of 2 or more to be included in the study. A significant number of patients had previous experience with cannabis. Forty percent of subjects assigned treatment with nabiximols showed a ≥ 30% reduction in self-reported spasticity using an 11-point *subjective* numerical rating spasticity scale (sNRS) compared to subjects assigned to placebo (21.9%) (difference in favour of nabiximols = 18%; 95% CI = 4.73, 31.52; p = 0.014). Mean number of sprays per day was 9.4 (~25 mg THC and ~24 mg CBD). Subjects on placebo or nabiximols exhibited similar incidences of adverse effects, but adverse CNS effects were more common with the nabiximols group. The majority of adverse events were of mild or moderate severity (e.g. dizziness, fatigue, depressed mood, disorientation, dysgeusia, disturbance in attention, blurred vision).

An observational, prospective, multicenter, non-interventional, clinical practice study examined the safety and effectiveness of nabiximols in the treatment of symptoms associated with MS (i.e. the **MO**bility impro**VE**ment in MS-induced spasticity study, **MOVE 2**) [690]. MS patients were followed over a three- to four-month period on outcomes, tolerability, QoL and treatment satisfaction. Prior to initiation on nabiximols, other anti-spastic medications were tried in 90% of study patients and the majority of the patients in the study (73%) were put on nabiximols. The mean number of nabiximols sprays/day was 6.9 (range: 1 – 12) reported at follow-up period 1, and 6.7 (range: 1 – 16) reported at follow-up period 2. Physician-based assessment of patients suggested a one-month course of treatment with nabiximols provided relief of resistant MS spasticity in the majority of patients who were administered the drug. After a one-month period, there was an initial response for spasticity detected in 42% of patients and a clinically relevant response for spasticity detected in 25% of these patients. At three-months' time, an initial response for spasticity was detected in 59% of patients and a clinically relevant response for spasticity detected in 40% of these patients. Scores in mean sleep disturbance decreased by 33% over a one-month treatment period in patients with an initial response, and by 40% in patients with a clinically relevant response. Scores on the combined modified Ashworth score (cMAS) decreased by 12% after one-month treatment in patients with an initial response and by 15% in patients with a clinically relevant response. Scores on the MSQoL-54 physical health composite scale and the mental health composite score showed statistically significant improvements over the three-month period in patients with an initial response and a clinically relevant response. After three-months' treatment with nabiximols, the mean EQ-5D-3L index value remained stable and a statistically significant reduction was observed in the percentages of patients considering muscle stiffness, restricted mobility, pain, and bladder disorders as most disturbing symptoms. Overall, at three-months' treatment time, almost 80% of the entire study population of patients on nabiximols was either "completely satisfied" or "satisfied" with the effectiveness of nabiximols. Most commonly observed adverse events with nabiximols were dizziness (4%), fatigue (2.5%), drowsiness (1.9%), nausea (1.9%), and dry mouth (1.2%).

A 12-month prolongation study of the **MOVE 2** clinical trial to determine long-term effectiveness and safety of nabiximols in clinical practice reported that from among 52 patients enrolled in the study that were included in the effectiveness analysis, the mean spasticity numerical rating scale score decreased significantly from 6.0 points at baseline to 4.8 points after one month and remained at this level after the 12-month period, including in patients who were classified as "initial responders" [691]. At baseline, the mean sleep disturbance numerical rating scale (NRS) score was 5.1 points in the subsample of participants and after 12 months it decreased to 3.2 points; in patients with an initial response, scores dropped from 5.4 to 2.4, and in patients with a clinically relevant response mean sleep disturbance NRS scores decreased from 5.3 to 1.9 points. Furthermore, the mean values of the MSQoL-54 physical health composite score and the mean mental health composite score both showed improvements, but were not statistically significant. The EQ-5D-3L index value showed improvement over the 12-month period for those patients who showed an initial and clinically relevant response. Furthermore, at study end, fewer patients who showed an initial and clinically-relevant response considered the MS spasticity-related symptoms of muscle stiffness, pain, restricted mobility, fatigue, and bladder disorders as the most disturbing symptoms compared to baseline. From the patient's perspective, impairment of daily activities was significantly improved after 12-month treatment with nabiximols compared to baseline and fewer patients complained about daily impairment of activities and notably, the improvement was more prominent in responders than in the entire study group. The majority of patients did not report adverse events. Most commonly reported adverse events included GI disorders, psychiatric disorders, and nervous system disorders. Mean daily number of nabiximols sprays was 6.2 (range: 2 – 12) and at least one other anti-spastic drug was still prescribed in 28 patients (e.g. baclofen, tizanidine, tolperisone, or gabapentin).

A pilot, prospective, multicentre, non-interventional post-marketing surveillance study conducted to collect data on driving ability, tolerability and safety from 33 patients with MS starting nabiximols treatment reported that a four to six-week treatment period with nabiximols (average 5.1 sprays per day, or 13.7 mg THC and 12.8 mg CBD/day) was associated with a statistically significant improvement in *self-rated* spasticity and was also <u>not</u> associated with a statistically significant deterioration in patients' ability to drive, as measured in the laboratory using a battery of cognitive and psychomotor tests [692]. However, less than half of the patients met the "fit to drive" criteria. In addition, 4 out of the 33 patients experienced a non-serious, mild or moderate adverse event associated with nabiximols treatment (e.g. dizziness and vertigo).

A non-randomized, non-placebo-controlled study quantitatively assessed the functional effects of nabiximols treatment on gait patterns in 20 patients with MS [693]. Enrolled MS patients had an expanded disability status scale (EDSS) score of 5.3 at study start, were unresponsive to spasticity treatments, and were able to walk unaided for 6 min. Patients were treated with nabiximols for one month (average number of sprays per day = 5.6 or a daily dose of 15 mg THC and 14 mg CBD) and the study reported that nabiximols treatment was associated with statistically significant improvements in Gait Profile Score, speed, cadence and stride length.

A four-week, prospective, randomized, double-blind, placebo-controlled, crossover clinical study of 44 patients with progressive primary or secondary MS, with moderate to severe spasticity and inadequate response to anti-spasticity agents investigated nabiximols-induced changes in neurophysiological measures of spasticity in patients with lower limb MS-associated spasticity, as well as changes in spasticity and related functional parameters [694]. At baseline, patients were concomitantly using glatiramer acetate, cyclophosphamide, azathioprine, fingolimod, natalizumab, interferon beta-1b, interferon beta-1a and methotrexate. Other medications included baclofen, eperisone, tizanidine, and benzodiazepines. Average daily dose of nabiximols was seven sprays per day or 18.9 mg THC and 17.5 mg CBD. The study reported no significant difference in the change from baseline to week 4 in the neurophysiological measure of spasticity (H/M ratio) with either nabiximols or placebo. Furthermore, no significant effect was found for all secondary neurophysiological measures. However, there was a statistically significant improvement in mean lower limb modified Ashworth scale score with nabiximols compared to placebo. There were no statistically significant differences for functional outcomes (timed 10 meter walk, 9-Hole Peg Test scores, pain NRS scores, sleep NRS scores, and Fatigue Severity Scale scores) between nabiximols and placebo. Most patients experienced an adverse event; the most commonly reported one was mild to moderate dizziness (21%), followed by lower limb weakness, vertigo, hypotension, hypertension, somnolence, and pharyngodynia. Most side effects were transient and appeared mostly during the titration phase or during increases in the number of sprays and resolved after reduction in the number of sprays. Limitations of the study included small sample size, short treatment period and relatively large number of study dropouts (14%) which limited the statistical power of the study.

A one-year, prospective, cohort study of 144 patients with moderate-to-severe MS spasticity and with evidence of inadequate response to traditional anti-spastic medications explored the efficacy, safety and tolerability of nabiximols at 4, 14, and 48 weeks and also assessed whether baseline demographic and clinical features could predict treatment response [695]. Patients were initially enrolled in a four-week "titration phase" to identify responders showing at least a 20% reduction in sNRS from baseline. Responders were then subsequently enrolled in the study. sNRS score dropped significantly in responders from 7.6 (baseline) to 5.2 at four weeks, with the mean number of daily sprays being 6.5 in responders vs. 7.7 in non-responders. sNRS score further improved in the responder group to a score of 5.0 (or a 30% clinically significant reduction in sNRS score) between 4 and 14 weeks' treatment. The cMAS was 4.0 at baseline in responders and significantly improved at four weeks' time and was persistently lower at 14 weeks' time compared to baseline. Nabiximols treatment was also associated with a significant improvement in the 10 min walking test after four weeks' treatment and improvement was maintained at 14 weeks compared to baseline. The ambulation index also showed a significant improvement in responders at 4 weeks and was maintained at 14 weeks despite an EDSS score that remained unchanged throughout the study period. Pain numerical rating score (pNRS) in responders showed a statistically significant decrease from 4.2 at baseline to 3.3 after 4 weeks' treatment and decreased further to 2.9 at 14 weeks. In responders who remained in the study at the 48-week follow-up, nabiximols efficacy was maintained with a spasticity score that remained statistically and clinically significantly lower than at baseline (i.e. 33% reduction) and the mean number of sprays taken daily was 6.2. Improvement in median cMAS was still evident, with a score of 3.0 at 48 weeks compared to 4.0 at baseline. The score on the pNRS was consistently lower at 48 weeks compared to baseline. No further improvement was noted for either the 10 min walking test or ambulation index. Eighty percent of patients in the study reported side effects, which appeared at a mean daily dose of 7.2 sprays (19.44 mg THC and 18 mg CBD). The most commonly reported side effects were confusion/ideomotor slowing (35%), dizziness (24%) and fatigue (20%). The majority of the reported side effects developed during the titration phase, were mild in intensity, and decreased with dosage adjustment. Nine percent of all patients enrolled in the study (responders and non-responders) discontinued treatment within 4 weeks of starting nabiximols because of side effects, while 9% of responders discontinued treatment for the same reason within 14 weeks of initiating treatment. One subject reported depersonalization two months after starting nabiximols while another subject developed depression. Lastly, demographic analysis suggested that patients with shorter disease duration and younger age tended to respond more favourably to nabiximols (i.e. "responders"). Study limitations included observational design, limited sample size, and lack of assessment of QoL and impairment in daily living.

CUPID and MUSEC clinical studies

The **C**annabinoid **U**se in **P**rogressive **I**nflammatory Brain **D**isease (**CUPID**) 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. 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. The **CUPID** trial found no evidence to support an effect of Δ^9-THC on MS progression, as measured by using either the EDSS or the MS 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 [696].

A double-blind, placebo-controlled, phase III clinical study (the **MU**ltiple **S**clerosis and **E**xtract of **C**annabis trial, **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 [697]. 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. 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 mild to moderate and did not persist beyond the study period. 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. 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 GI 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 [278]. The study, a double-blind, placebo-controlled, crossover clinical 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). Smoking cannabis was also associated with a statistically significant reduction in patient scores on the VAS for pain, although patients reportedly had low levels of pain to begin with. No differences between placebo and cannabis were observed in the timed-walk task, a measure of physical performance. Cognitive function, as assessed by the Paced Auditory Serial Addition Test, 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. 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. 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.

Cannabis/cannabinoid tolerability in multiple sclerosis

Generally speaking, cannabis and orally administered prescription cannabinoids (e.g. dronabinol, nabilone, nabiximols, Cannador®) are reported to be well tolerated in patients with MS [686, 690-692, 694, 695, 698, 699]. Clinical trials to date do not indicate serious adverse effects associated with the use of these prescription cannabinoid medications (or cannabis). 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 [387, 699].

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 [233]. Another cross-sectional study reported that while patients with MS who smoked cannabis daily are more cognitively impaired than non-users especially with respect to working memory, attention and information processing speed, no structural differences (lesion volume, global atrophy, diffusion tensor imaging [DTI] metrics) were discernible between users and non-users [700]. However, a follow-up study suggested that in the same cannabis-smoking patients, but not in the non-users, volume reductions in gray matter and white matter (in medial and lateral temporal regions, thalamus, basal ganglia, prefrontal cortex) were associated with the observed widespread cognitive deficits [701].

In contrast, another study concluded that nabiximols treatment, in cannabis-naïve MS patients, was not associated with cognitive impairment [699]. 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 in MS patients, and more generally in patients using for therapeutic purposes.

Bladder dysfunction associated with multiple sclerosis or spinal cord injury

Bladder dysfunction occurs in most patients suffering from MS or SCI [702]. The most common complaints are increased urinary frequency, urgency, urge, and reflex incontinence [703]. cannabinoid receptors are expressed in human bladder detrusor and urothelium [37, 38], and may help regulate detrusor tone and bladder contraction as well as affecting bladder nociceptive response pathways (reviewed in [38]).

An early 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 [538]. A sixteen-week, open-label, pilot study of cannabis-based extracts (a course of nabiximols 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 [704]. Improvements were also noted in patient self-assessments of pain and quality of sleep. A subsequent RCT of 250 MS patients suggested a clinical effect of orally administered cannabinoids (2.5 mg Δ^9-THC or 1.25 mg CBD with < 5% other cannabinoids per capsule, up to a maximum 25 mg/day) on incontinence episodes [702].

4.5.2 Amyotrophic lateral sclerosis

There is some pre-clinical evidence implicating the ECS in the progression of an ALS-like disease in mouse models of the disorder; under certain conditions, cannabinoids, or elevation of endocannabinoid levels through pharmacological inhibition or genetic ablation, have been reported to modestly delay disease progression and prolong survival in these animal models (reviewed in [705].

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 [706, 707].

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 to

10 mg per day of dronabinol (Δ^9-THC) were associated with improvements in sleep and appetite, but not cramps or fasciculations [708]. In contrast, a shorter two-week study reported no improvement in these measures in ALS patients taking 10 mg of dronabinol per day [707]. In either case, dronabinol was well-tolerated with few reported side effects in this patient population at the tested dosages.

4.5.3 Spinal cord injury (or spinal cord disease)

Pre-clinical animal studies have shown the existence of an ECS in the spinal cord and a basal endocannabinoid tone in non-injured spinal cords [709]. While the role of the ECS in the intact spinal cord is only partially known, endocannabinoids modulate spinal cord analgesia as well as excitability, participating in the physiological control of reflexes [709]. Pre-clinical animal studies suggest that SCI triggers changes in the activity of the ECS, with an acute spike in production of anandamide and 2-AG in the epicenter of the damaged area [709]. The spike in endocannabinoid levels, reflecting an active protective process induced by injury, returns to basal levels within a few days' post-injury; however 2-AG levels go through a subsequent secondary and more protracted rise in levels over a subsequent 28-day period [709]. Blocking both CB_1 and CB_2 receptors worsens SCI-associated damage, whereas stimulation of these two cannabinoid receptors appears to be protective and may also alleviate neuropathic pain associated with SCI [710-712]. One pre-clinical study also reported a beneficial effect of CBD in restoring motor function and reducing extent of injury following SCI in a mouse model [713]. Subjective improvements have been anecdotally reported by SCI patients smoking cannabis [642, 714]

However, despite the evidence from animal studies and anecdotal claims, limited clinical information exists regarding the use of cannabis and cannabinoids to treat symptoms associated with SCI such as pain, spasticity, muscle spasms, urinary incontinence, and difficulties sleeping. Double-blind, crossover, placebo-controlled studies of oral Δ^9-THC and/or nabiximols suggested modest improvements in pain, spasticity, muscle spasms, and sleep quality in patients with SCI [642, 715, 716]. More recently, a randomized, double-blind, placebo-controlled parallel study using a minimum of 15 to 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 SCI [717] and a 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 SCI [718].

A recent randomized, double-blind, placebo-controlled, cross-over clinical trial of vapourized cannabis showed analgesic and anti-spastic benefit for patients with SCI and disease [276]. In this clinical trial, 42 patients (the majority of whom were currently using or had used cannabis) with neuropathic pain from SCI and disease were administered between 8 and 12 inhalations of cannabis placebo, or cannabis containing either low (2.9%) strength THC or high (6.7%) strength THC over an 8 h treatment session (400 mg dried cannabis material; vapourization temperature 185 ºC). While 400 mg of dried cannabis was placed in the vapourizer, only 45.9 mg (range: 29.9 – 83.8 mg) of the lower strength and 56.3 mg (range: 15.7 – 172.9 mg) of the higher strength cannabis was vapourized. These amounts and strengths suggest that on average between 1.3 and 3.8 mg of THC may have been inhaled (range: 0.86 – 11.6 mg THC). Median blood plasma concentrations of THC were 23 ng/mL (peak: 68.5 ng/mL) for the 2.9% strength and 47 ng/mL (peak: 177 ng/mL) for the 6.7% strength 3 h after an initial round of four inhalations and immediately after a second round of between four and eight additional inhalations. Pain intensity (primary outcome) decreased with increasing THC strength and was statistically significantly different from placebo for both strengths of THC after the first hour of exposure (round 1: 4 inhalations) and improved further compared to placebo after a second-round of inhalations (an additional 4 to 8 inhalations for a total of 8 to 12 inhalations overall). Pain relief showed a statistically significant difference between low and high strengths compared with placebo. The number of patients needed to treat (NNT) to achieve a 30% reduction in pain during the 8 h treatment session was 4 for the lower (2.9%) strength and 3 for the higher (6.7%) strength compared to placebo, whereas the NNT was 6 when comparing between the lower and higher strengths (but CIs were wide). By comparison, for neuropathic pain the NNT for pregabalin is 3.9 and for gabapentin, 3.8. Both strengths of cannabis provided statistically significant improvements on a variety of pain descriptors (i.e. sharpness, burning, aching, cold, sensitivity, unpleasantness, deep pain and superficial pain) but only the higher strength provided short-term relief of itching. No general effect was noted on allodynia. Only the lower strength (2.9%) was associated with a statistically significant decrease in spasticity and only 3 h after treatment initiation. Generally, there were no statistically significant differences between study medications on various measures of neuropsychological performance. Many of the psychoactive effects ("high", "good drug effect", "any drug effect", "impaired", "stoned", and "sedated") showed a dose dependency with greater effects with the higher dose compared to the lower dose and with both doses compared to placebo. The authors suggest that patients with SCI or disease who wish to avoid the psychomimetic effects while benefiting from the therapeutic effects consider using the lower dose (2.9%).

4.6 Epilepsy

- ***Anecdotal evidence suggests an anti-epileptic effect of cannabis (THC- and CBD-predominant strains).***
- ***The available evidence from pre-clinical and limited clinical studies suggests certain cannabinoids (CBD) may have anti-epileptiform and anti-convulsive properties, whereas CB_1R agonists (THC) may have either pro- or anti-epileptic properties.***
- ***However, the clinical evidence for an anti-epileptic effect of cannabis is weaker, but emerging, and requires further study.***
- ***Evidence from clinical studies with Epidiolex® (oral CBD) suggests efficacy and tolerability of Epidiolex® for drug-resistant seizures in treatment-resistant Dravet syndrome or Lennox-Gastaut syndrome.***
- ***Evidence from observational studies suggests an association between CBD (in herbal and oil preparations) and a reduction in seizure frequency as well as an increase in quality of life among adolescents with rare and serious forms of drug-resistant epilepsy.***
- ***Epidiolex® has received FDA approval (June 2018) for use in patients 2 years of age and older to treat treatment-resistant seizures associated with Dravet syndrome and Lennox-Gastaut syndrome.***

Epilepsy is one of the most common neurological disorders with a worldwide prevalence of approximately 1% [217, 719]. It is not a singular disease entity, but a variety of disorders reflecting underlying brain dysfunction arising from many different causes [720]. Epilepsy is characterized by recurrent, unprovoked seizures, which are transient occurrences of signs and symptoms caused by abnormal excessive or synchronous neuronal activity in the brain [720]. Seizures can be of various types including genetic and occurring in childhood (e.g. Dravet Syndrome, Lennox-Gastaut), or acquired and occurring in adulthood (e.g. after severe head injury, stroke, or from a tumour) [265]. Co-morbidities associated with epilepsy include cognitive decline, depressive disorders, and schizophrenia [721].

Despite the availability of many anti-epileptic medications, close to 30% of patients with epilepsy remain refractory to conventional treatments leading them to search for other therapeutic modalities, such as cannabis (e.g. CBD-enriched cannabis oils) [722].

The endocannabinoid system and epilepsy

The ECS is known to regulate cortical excitability, and endocannabinoids have been suggested to produce a stabilizing effect on the balance between excitatory and inhibitory neurotransmitters in the CNS [723].

Temporal lobe epilepsy, one of the most common kinds of epilepsy seen in adults, is associated with changes in the hippocampus where CB_1 receptor expression is downregulated during the acute phase, shortly after the precipitating insult, but then upregulated in the chronic phase of the disorder [217, 265, 724, 725]. Furthermore, it appears that the expression of the CB_1 receptor on excitatory glutamatergic axon terminals, as well as the expression of DAGL, which is responsible for yielding the endocannabinoid 2-AG, are both downregulated [265]. In contrast, CB_1 receptor expression on inhibitory GABAergic axon terminals appears to be upregulated. In addition, reduced levels of the endocannabinoid anandamide have been detected in the cerebrospinal fluid (CSF) of patients with untreated, newly diagnosed, temporal lobe epilepsy [726], whereas normally, anandamide is found in high concentrations in the hippocampus, a brain region known to be involved in epileptogenesis and seizure disorders [263]. Taken together, these and other studies demonstrating changes in CB_1 receptor and DAGL expression in the hippocampus and changes in anandamide levels [727-729] suggest important and widespread changes in the functioning of the ECS in epilepsy. Since the ECS is generally thought to act as a neurotransmitter braking system, the reported dysregulation of the ECS in epilepsy may play a role in the generation and maintenance of epileptic seizures [265]. There is also some evidence to suggest that endocannabinoids promote the maintenance, but not the initiation, of epileptiform activity by activating CB_1 receptors located on astrocytes [730].

Pre-clinical studies

In vitro and *in vivo* studies suggest certain phytocannabinoids (and endocannabinoids) can have anti-convulsive but also, in some cases, pro-convulsive roles [263, 265, 266, 719, 721, 731-739].

CB_1 receptors are located mainly pre-synaptically where they typically inhibit the release of classical neurotransmitters [740].The purported anti-epileptic effect of certain cannabinoids (e.g. THC) is thought to be mediated by CB_1-receptor dependent pre-synaptic inhibition of glutamate release [265, 728, 741]; on the other hand, epileptogenic effects may be triggered by pre-synaptic inhibition of GABA release [265, 736, 739, 742-744]. CB_1 receptor agonists (e.g. THC) 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) [112, 266, 741]. Because of the ability of CB_1 receptor agonists such as THC to yield either pro- or anti-convulsant activities and because of the reported development of tolerance to their anti-convulsant effects, CB_1 receptor agonists are thought to be unlikely to yield therapeutic benefit for patients with epilepsy [263, 266].

In contrast to the ambiguous situation with CB_1 receptor agonists such as THC, phytocannabinoids such as CBD, CBDV, THCV, and CBN appear to mainly have anti-convulsant roles and may have more potential therapeutic value for the treatment of epilepsy [263, 266]. A number of *in vivo* studies have demonstrated the anti-epileptic effects of CBD across different animal models of epilepsy (reviewed in [263]). Early studies using various rat and mouse models of epilepsy reported that CBD was an effective anti-convulsant and its potency was significantly increased when combined with anti-epileptic drugs such as phenytoin and phenobarbital used to treat major seizures [263, 745]. In contrast, CBD reduced the anti-convulsant potencies of chlordiazepoxide, clonazepam, trimethadione, and ethosuximide used for minor seizures [263, 745]. ED_{50} doses for CBD in rats ranged from as low as 12 mg/kg (p.o.) to as high as 380 mg/kg (i.p.) in mice [263, 745, 746]. Another study reported that CBD attenuated epileptiform activity *in vitro* in hippocampal slices and displayed anti-convulsant activity *in vivo* (100 mg/kg) in one rat model of epilepsy, attenuating seizure severity, tonic-clonic seizures and mortality [735]. A follow-up study by this same group examined the anti-convulsive effects of CBD in two other rat models of temporal lobe and partial epilepsy [733]. CBD at doses of 1, 10, and 100 mg/kg significantly attenuated the percentage of animals displaying seizure events (temporal lobe epilepsy); however, there was no significant effect upon the mean number of seizure occurrences per animal or on seizure severity. In the model of partial seizure, CBD (1, 10, 100 mg/kg) decreased the percentage of animals that developed tonic-clonic seizures and was associated with decreased mortality rate (at 10 and 100 mg/kg), but had no effect on overall seizure severity. CBD was also reported to have some minor negative effects on motor function at a dose of 100 mg/kg, which was paradoxically attenuated when the dose was doubled (200 mg/kg) [733].

The anti-convulsant effects of pure CBDV as well as botanical extracts containing CBDV (and significant amounts of CBD), with and without THC and THCV, have been investigated in a number of animal models of epilepsy [263, 719, 721, 747]. CBDV (> 10 μM) was found to significantly attenuate epileptiform activity *in vitro* as well as having significant anti-convulsant effects *in vivo* (min. > 50 mg/kg i.p.) in different mouse models of epilepsy [747]. A dose of 200 mg/kg (i.p.) of CBDV was associated with complete cessation of tonic convulsions in two models of epilepsy and attenuated seizure severity and mortality at a 200 mg/kg i.p. dose as well as significantly delaying seizure onset in a third epilepsy model [747]. Furthermore, co-administration of CBDV and the anti-epilepsy drugs valproate, ethosuximide, or phenobarbital was associated with significant anti-convulsant effects [747]. For example, co-administration of CBDV (200 mg/kg) with valproate (50 – 250 mg/kg) or ethosuximide (60 – 175 mg/kg) was associated with significant anti-convulsant effects [747]. Co-administration of 200 mg/kg CBDV and phenobarbital (10 – 40 mg/kg) was also associated with significant anti-convulsant effects [747]. CBDV did not appear to have any significant effects on motor performance at the tested doses and also appeared to be well-tolerated when co-administered with these anti-epileptic drugs [747]. In mice and rats, CBDV showed significant anti-convulsive effects with doses ranging from 50 mg/kg to 400 mg/kg or more [263, 719, 721]. Furthermore, *in vivo* animal studies with two types of botanical extracts enriched in CBDV (47.4 – 57.8 %) and CBD (13.7 – 13.9%) with and without THC (1%) and THCV (2.5%) were studied for their anti-convulsive effects as well as their toxicities [721]. The study found that both botanical extracts showed similar significant anti-convulsive actions in three different animal models of epilepsy and that the presence of THC/THCV at the doses administered in the extracts did not contribute to the anti-convulsive actions [721]. On the other hand, the presence of THC/THCV in the extract contributed to some observed adverse motor effects [721]. Lastly, CBDV was found to bind only weakly to the CB_1 receptor, suggesting the anti-convulsant mechanism of action of CBDV is CB_1-receptor independent [721].

In contrast with CBD and CBDV, the anti-convulsant effects of CBN have not been as well studied. In one study, CBN produced anti-convulsant effects with an ED_{50} of 18 mg/kg [263, 745].

Although *in vitro* studies show that THCV binds with relatively high affinity at CB_1 receptors [112, 748], THCV does not appear to be a potent CB_1 receptor agonist [112, 263, 748]. Instead, experimental studies suggest THCV acts more like a CB_1 receptor antagonist and a potent CB_2 receptor partial agonist [18, 112, 263, 748, 749]. At higher doses however, THCV appears to have some agonist activity at the CB_1 receptor [18]. Furthermore, *in vitro* studies suggest THCV has some anti-epileptiform effects at micromolar concentrations [112] and *in vivo* studies suggest THCV (0.25 mg/kg) has some limited anti-convulsant effects in one mouse model of epilepsy [112, 266].

There is little experimental evidence thus far for the anti-convulsant effects of CBG. While one *in vitro* study suggests anti-epileptiform activity for CBG, an *in vivo* study in rats suggests that in one model of epilepsy, CBG (at doses ranging from 50 – 200 mg/kg) does not have anti-convulsant effects [263, 750].

Data from observational studies and patient surveys

According to some studies, about 20% of epilepsy patients are actively using cannabis [722, 731, 751, 752]. A telephone survey of 136 patients of a Canadian tertiary care epilepsy centre revealed that 48% had used cannabis in their lifetime, 21% were active users, 13% were frequent users (one day per week or more), and 8.1% were heavy users (every other day or more) [752]. Three percent of subjects met the criteria for cannabis dependence. When asked about their personal experiences with cannabis use, 68% of respondents said their seizure severity improved, while 32% said there was no effect. With regard to seizure frequency, 54% claimed improvement, while 46% stated no effect. Eleven percent noted fewer side effects from medications when using cannabis, while 85% did not notice an effect. Forty-three percent of respondents stated medical reasons for cannabis use. The survey authors noted that cannabis use was associated with increased seizure frequency and longer duration of disease. While the reasons for these associations is not clear, it is possible that patients with more severe epilepsy are more prone to trying or using cannabis or that cannabis use is associated with worsening epilepsy.

Another study interviewed epilepsy outpatients at a tertiary epilepsy clinic in Germany. Out of 310 epilepsy patients that were interviewed, 28% said they had used cannabis in their lifetime while 63% had consumed cannabis after their epilepsy diagnosis [751]. Almost 70% of epilepsy patients had partial epilepsy, a little over 20% had idiopathic generalized epilepsy, and approximately 10% were undetermined. Common reasons for cannabis use included curiosity, enjoyment and relaxation. The majority of patients (84%) who had started using cannabis after their epilepsy diagnosis did not observe any effect on their epilepsy, 5% had reported improvement in their seizures or symptoms associated with cannabis use, and 11% reported worsening of seizures associated with cannabis use.

A retrospective clinical chart review of 18 Canadian patients with epilepsy who were authorized to possess cannabis for medical purposes reported that 61% had focal epilepsy, with 39% having generalized epilepsy [753]. Twenty-two percent had mesial temporal sclerosis, 17% had idiopathic epilepsy, 17% had epilepsy associated with a tumour, 11% had been diagnosed with Lennox-Gastaut, 11% had epilepsy associated with a congenital malformation, and 11% were classified as unknown. Psychiatric comorbidity was common (61%) with depression being the most frequent entity. Most patients had used an average of five anti-epileptic medications in the past. Eighty-nine percent of patients had a long history of cannabis use before obtaining an authorization to possess. Mode of administration was mainly by smoking (83%). Mean number of daily puffs was 4 and the estimated amount of cannabis consumed per day was 2 g. All patients that stopped cannabis use reported exacerbation of seizures associated with drug withdrawal. None reported status epilepticus as a complication. One hundred percent of patients reported improvement in seizure severity and seizure frequency. Eighty-nine percent of the patients reported no side effects, while all reported an improvement in mood disorders, and general well-being. Eighty-nine percent reported an improvement in sleep quality and appetite. Limitations of this study included its retrospective nature and bias associated with self-reporting, as well as the lack of a control group and its small sample size.

Treatment-resistant, childhood-onset epilepsy

The results from two parent surveys of children with treatment-resistant childhood epilepsy and who tried cannabis oils have been published and are summarized here [215, 264]. In one survey of 19 children, 13 had Dravet syndrome, 4 had Doose syndrome, 1 had Lennox-Gastaut and 1 had idiopathic early-onset epilepsy [264]. Children ranged in age from 2 to 16 years. The parents reported that the children had a variety of different seizure types including focal, tonic-clonic, myoclonic, atonic, and infantile spasms. In virtually all cases, the study reported that the children had treatment-resistant epilepsy for more than three years before trying CBD-enriched cannabis. The children had tried an average of 12 other anti-epileptic medications before beginning CBD-enriched cannabis treatment. Dosages of CBD reported ranged from less than 0.5 mg/kg/day to 28.6 mg/kg/day, while dosages of THC were reported to range from 0 to 0.8 mg/kg/day. Duration of CBD-enriched cannabis use was reported to range from two weeks to over one year. Eighty-four percent of the parents that responded to the survey reported a reduction in their child's seizure frequency. Two parents reported a complete halt of seizures in their children after more than four months of treatment. Forty-two percent of the surveyed parents reported a greater than 80% reduction in seizure frequency, 16% reported a greater than 50% reduction in seizure frequency and the same proportion of parents reported a greater than 25% reduction as well as no reduction. Sixty-percent of parents reported weaning their child from another anti-epileptic medication after starting CBD-enriched cannabis treatment. Parent-reported beneficial effects included better mood (79%), increased alertness (74%), better sleep (68%), and decreased self-stimulation (32%), while adverse effects included drowsiness (37%), and fatigue (16%). Limitations of such a survey include the self-selection bias, lack of a control group, the inability to independently verify any of the parents' claims including information about dosing, as well as the small sample size and the under-representation of epilepsy types other than Dravet syndrome.

The results of a second parent survey [215] have also been published. In this survey, 117 parents of children with treatment-resistant epilepsy responded. Forty-five percent of parents reported a child with infantile spasms and/or Lennox-Gastaut syndrome, while 13% reported severe myoclonic epilepsy of infancy (Dravet syndrome). Four percent reported myoclonic-astatic epilepsy (Doose syndrome) and 38% reported other types of epilepsy. Age range of children was 3 to 10 years and the median number of anti-epileptic medications tried and failed prior to trial of CBD-enriched cannabis preparations was eight. Median duration of CBD treatment was 6.8 months (range: 3.8 to 9.8 months). Median dosage of CBD in the preparations was 4.3 mg/kg/day (range: 2.9 to 7.5 mg/kg/day). The vast majority of respondents reported using CBD-enriched oil-based extracts, typically administered two to three times per day. The reported CBD to THC ratio in the oil preparations was at least 15:1. Eighty-five percent of respondents reported a reduction in seizure frequency, including 14% reporting complete seizure freedom while 9% reported no change and 4% reported an increase in seizure frequency. Eighty-six percent of respondents reported either an improvement or worsening within 14 days of starting treatment. Adverse effects associated with treatment included increased appetite (29.9%) and weight gain (29.1%). Interestingly, the median number of side effects reported during treatment was much lower than that reported before treatment. The reported decrease in the number of side effects during treatment was attributed to the claimed discontinuation of at least one anti-seizure medication during treatment. While overall, the prevalence of adverse effects was decreased during treatment with the cannabis preparations, the most often encountered adverse effects were drowsiness (12.8%), fatigue (9.4%), irritability (9.4%), and nausea (6.8%). Respondents reported improvement in sleep (53%), alertness (71%), and mood (63%). Again, as with the survey carried out by Porter et al., the survey by Hussain et al. 2015 carries the same limitations and the data must be interpreted with caution.

A retrospective chart review of 75 children and adolescents in Colorado who were given oral cannabis extracts for the treatment of refractory epilepsy reported that 57% of patients showed improvement in seizure control and 33% reported a > 50% reduction in seizures [754]. Average age was 7.3 years (range: 6 months to 18 years) when starting oral cannabis extract treatment. Four percent of the patients had Doose syndrome, 17% had Dravet syndrome, and 12% were diagnosed with Lennox-Gastaut syndrome. Among children with a specified syndrome, those with Lennox-Gastaut represented the greatest proportion of responders to oral cannabis extracts (89%), followed by those with Dravet syndrome (23%) and those with Doose syndrome appeared to respond the least (0%). When classified by seizure type, those with atonic seizures appeared to have the greatest response rate (44%), followed by those with focal (38%) and epileptic spasms (36%), generalized tonic-clonic (30%), absence (28%), myoclonic (20%), and tonic (17%) [215]. Reported improvements included an increase in alertness/behavior (33%), language (11%), motor skills (11%), and sleep (7%). Adverse events were reported in 44% of patients treated with an oral cannabis extract. Adverse effects associated with oral cannabis extract administration included worsening of seizures (13%), somnolence (12%), GI symptoms (11%), and irritability (5%). Surprisingly, there were no reported differences in response based on the strain or type of oral cannabis extract the patients were treated with (i.e. high CBD, CBD plus other oral cannabis extracts, THCA, and other oral cannabis extract types). The majority of patients used an oral cannabis extract with high CBD content with or without other oral cannabis extracts. Study limitations included small sample size, heterogeneity of products used, uncertain dosages of cannabinoids, inability to determine dose-response, and discrepancy in ratings of treatment benefit between families that had moved to Colorado for treatment vs. those that were state residents.

A retrospective, multicenter study examined the effect of CBD treatment for severe intractable epilepsy (i.e. acquired epilepsy, early epileptic encephalopathy with known genetic etiology, epileptic encephalopathy with unknown genetic etiology, congenital brain malformation, hypoxic ischemic encephalopathy, and other, with resistance to five to seven anti-epileptic medications, ketogenic diet and vagal nerve stimulation) [213]. The study examined the clinical records of clinic and phone call visits of children and adolescents (age range: 1 – 18) with refractory epilepsy being treated in four pediatric epilepsy centres in Israel. Seventy-four children and adolescents were included in the study and the reported daily dose of CBD (1 – 20 mg/kg/day) was administered over an average period of six months (minimum three months). Highest daily CBD dose was 270 mg/day. Eighty percent of the children included in the study used less than 10 mg/kg/day CBD with the remainder (20%) using more than 10 mg/kg/day CBD. The ratio of CBD to THC was 20 : 1 and cannabinoids were dissolved in canola oil. Parents or older children reported any changes in seizure number. CBD treatment was associated with a reduction in seizure frequency as well as improved behaviour and alertness, improved language, improved communication and motor skills and improved sleep. Approximately half of the patients reported side effects with 18% reporting seizure aggravation, 22% reporting somnolence or fatigue and 7% reporting GI problems or irritability. Side effects led to withdrawal of cannabis oil extract in five patients. Limitations of the study include retrospective design, lack of a control group, no consistent rate of dosage elevation, reliance on parental report of effect on seizure frequency, short duration of the study and lack of long-term outcome, lack of EEG results, and no measurement of other drug levels.

Clinical studies

Note: Epidiolex® is the brand name for a whole-plant cannabis extract of a high CBD strain of Cannabis sativa and is an oral oil solution product containing > 98% CBD at a concentration of 100 mg/ml. Epidiolex® has received FDA approval (June 2018) for use in patients 2 and older to treat Dravet syndrome and Lennox-Gastaut syndrome. It has also received Orphan Drug Designation in the U.S. for the treatment of Lennox-Gastaut Syndrome, Dravet Syndrome and Tuberous Sclerosis Complex. At the time of writing of this publication, Epidiolex® has not received a Notice of Compliance from Health Canada, and is not marketed in Canada.

While there are many anecdotal accounts of dramatic improvements with cannabis-based products with high CBD to THC (e.g. 20 > 1) ratios, the available clinical evidence supporting the safety and efficacy of cannabis for epilepsy is relatively sparse [217, 266, 671]. The available evidence from clinical studies is discussed below and summarized in a Cochrane review [217].

One randomized, placebo-controlled clinical study of nine individuals with uncontrolled temporal lobe epilepsy who had failed treatment with multiple anti-epileptic medications reported that two of the individuals that received daily doses of 200 mg of CBD for three months were seizure-free, one showed partial improvement and one did not show any improvement [217, 755]. None of the placebo-treated patients showed any signs of improvement. No adverse effects were noted. Limitations of this study included lack of comparison between the CBD-treated group and the placebo-group for baseline seizure characteristics, small sample size, unclear methodology, possible lack of blinding, and lack of statistical analysis.

Another randomized, placebo-controlled clinical study of 15 epileptic patients suffering from uncontrolled temporal lobe epilepsy reported that daily treatment with doses of 200 to 300 mg of CBD (in combination with a variety of conventional anti-epileptic drugs) lasting 3 to 18 weeks was associated with seizure cessation in four (out of eight) patients treated with CBD [217, 756]. One placebo-treated patient (out of seven) became seizure-free. Adverse reactions included somnolence. Limitations of this study included lack of comparison between the CBD-treated group and the placebo-group for baseline seizure characteristics, small sample size, unclear methodology, possible lack of blinding, and lack of statistical analysis.
One placebo-controlled clinical trial of 12 patients with frequent seizures who were not taking any anti-epileptic medications reported no statistically significant difference in seizure frequency between patients given daily doses of 200 to 300 mg of CBD for four weeks compared to placebo [217, 757]. Reported adverse effects included drowsiness. Limitations of the study included small sample size, possible unblinding, lack of comparison between the CBD-treated group and the placebo-group for baseline seizure characteristics, and unclear methodology.

A randomized, double-blind, placebo-controlled, cross-over clinical study of 12 patients with incompletely controlled epilepsy reported that treatment with 100 mg of CBD, three times daily, for six months, appeared to be associated with a decrease in seizure frequency although seizure frequency was not well measured and no statistical analysis was performed [217, 758]. CBD treatment also did not appear to be associated with any adverse behavioural changes. Limitations of this study included small sample size, lack of statistical analysis and lack of objective measurement of seizure frequency.

A Cochrane review of the clinical evidence for cannabinoid treatment for epilepsy reviewed the four clinical studies discussed above [755-758] and concluded that, based on their evaluation criteria, all of these reports were of low quality and no reliable conclusions could be drawn based on these studies regarding the efficacy of cannabinoids (CBD) as a treatment for epilepsy. However, a dose of 200 to 300 mg of CBD daily could be safely administered to small numbers of patients for short periods of time but the safety of long-term CBD treatment could not be reliably assessed in these studies [217].

Treatment-resistant, childhood-onset epilepsy

A clinical study investigating differences in ECS components and in molecular targets associated with CBD action found an increase in expression levels of the voltage-dependent calcium channel α-1h subunit, in CB_2 receptor gene expression, and a decrease in the expression of the serotonin transporter gene in lymphocytes isolated from Dravet Syndrome patients [759].

A report from an expanded access investigational new drug (IND) trial of Epidiolex®, an oil-based cannabis extract containing 98% v/v CBD, examined the interaction between clobazam and Epidiolex® (CBD) during the treatment of refractory pediatric epilepsy [236]. Thirteen subjects with refractory epilepsy were included in the study. Diagnoses included Dravet syndrome, Doose syndrome, cortical dysgenesis, isodicentric duplication chromosome 15q13, CDKL5 (Cyclin-Dependent Kinase-Like 5) mutation, Tuberous sclerosis complex, and lissencephaly. Seventy percent of the included patients had a > 50% decrease in seizures. Daily doses of Epidiolex® ranged from 5 mg/kg/day to a maximum of 25 mg/kg/day. The average daily dose of clobazam was 1 mg/kg/day with a range of 0.18 to 2.24 mg/kg/day. Co-administration of CBD and clobazam was associated with higher plasma levels of clobazam and its active metabolite n-desmethylclobazam and close monitoring of plasma levels of clobazam and n-desmethylclobazam is recommended as is dose adjustment of clobazam, as needed, to prevent overdose. Side effects were reported in 77% of the 13 study subjects and included drowsiness, ataxia, irritability, restless sleep, urinary retention, tremor and loss of appetite.

An expanded-access, prospective, open-label, 12-week clinical trial of Epidiolex® (98 – 99% CBD oil oral preparation, 100 mg/mL) in patients aged 1 to 30 years with severe, intractable, childhood-onset, treatment-resistant epilepsy (mainly Dravet and Lennox-Gastaut syndromes) examined whether addition of CBD to existing anti-epileptic treatment regimens would be safe, tolerated and efficacious [262]. Patients were started at a dose of CBD between 2 and 5 mg/kg/day divided into twice-daily dosing added to existing anti-epileptic treatments (i.e. ketogenic diet, clobazam, valproate), and slowly titrated upwards by 2 to 5 mg/kg once per week until intolerance or up to a maximum dose of 25 mg/kg per day (or up to a maximum of 50 mg/kg/day, depending on the study site). The maximum dose at the 12-week clinic visit was 41 mg/kg/day, and the mean CBD dose at 12 weeks was 23 mg/kg in the safety analysis group and in the efficacy analysis group. The median monthly frequency of motor seizures was 30 at baseline and 16 over the 12-week treatment period, and the median reduction in monthly motor seizures was 37%. The greatest reduction in seizures occurred in those patients with focal seizures (-55%) or atonic seizures (-54%), followed by tonic seizures (-

37%), or tonic-clonic seizures (-16%). Combination therapy (CBD with clobazam or valproate) was associated with a greater reduction in seizures compared to patients not using clobazam or valproate. Adverse events were reported in 79% of the patients within the safety group. Adverse events in more than 5% of patients were somnolence (25%), decreased appetite (19%), diarrhea (19%), fatigue (13%), convulsions (11%), appetite changes (9%), status epilepticus (8%), lethargy (7%), changes in blood concentrations of concomitant anti-epileptic drugs (6%), gait disturbance and sedation. Most adverse events were mild or moderate and transient. Serious adverse events deemed possibly related to CBD use (10%) included status epilepticus (6%), diarrhea (2%), pneumonia (<1%), and weight loss (1%). Patients taking more than 15 mg/kg/day CBD were more likely to report diarrhea or related side-effects (e.g. weight loss). Three percent of the enrolled patients withdrew from the study, and reasons for study withdrawal included allergy to the sesame oil vehicle, hepatotoxicity, excessive somnolence and poor efficacy, GI intolerance, worsening seizures, and hyperammonemia. Major limitations of this study included open-label design and lack of an appropriate control group. In addition, the issue of a significant placebo response was noted by the authors to be of special significance in pediatric trials of cannabis-based treatments. The authors note that the placebo response in RCTs of add-on treatments in patients with epilepsy appears to be more significant in the pediatric population compared to adults (19% vs. 9.9 – 15%).

A randomized, double-blind, placebo-controlled trial was conducted to determine the efficacy and safety of Epidiolex® in treating drug-resistant seizures in the Dravet syndrome [576]. After a 4-week baseline period, a total of 120 affected children and young adults (2.3 to 18.4 years old) were randomized (1:1) to receive either 20 mg/kg/day CBD oral solution or placebo, in addition to standard antiepileptic treatment, for 14 weeks (2 weeks of dose escalation and 12 weeks of dose maintenance). At the end of the treatment period there was a 10-day taper period (10% in dose reduction per day) followed by a 4-week follow-up period. The most common type of convulsive seizure was generalized tonic-clonic (78%) followed by secondarily generalized tonic-clonic seizures (21%). Nonconvulsive seizures were reported by 61% of the patients in the CBD group and 69% in the placebo group. Treatment with CBD decreased the median frequency of convulsive seizures per month (primary endpoint) from 12.4 (range: 3.9 to 1,717) to 5.9 (range: 0.0 to 2,159), while placebo had no effects (from 14.9 to 14.1). The adjusted median difference between the CBD and placebo groups in change in seizure frequency was -22.8 percentage points (95% CI = -41.1 to -5.4; p = 0.01). The effects of CBD on convulsive seizures were seen in the first month of the maintenance period. In the CBD group, 43% of the patients had at least a 50% reduction in the frequency of convulsive seizures compared to 27% in the placebo group (OR, 2.00; 95% CI = 0.93 to 4.30; p = 0.08). During the treatment period, 3 patients (5%) in the CBD group and no patients in the placebo group became seizure-free (p = 0.08). CBD decreased from 24.0 to 13.7 the median frequency of seizures per month (adjusted reduction 28.6%), while placebo decreased it from 41.5 to 31.1 (adjusted reduction 9.0%), for a significant adjusted median difference between groups of -19.2 percentage points (p = 0.03). There was no significant difference between groups for reduction in nonconvulsive seizures (p = 0.88). Common adverse events (>10% frequency) in the CBD group were somnolence (36%), diarrhea (31%), decreased appetite (28%), fatigue (20%), vomiting (15%), pyrexia (15%), lethargy (13%), upper respiratory tract infection (11%), and convulsion (11%). Most of them were mild or moderate in severity (84% in the CBD group) and considered related to the trial agent (75%). In the CBD group, 8 patients withdrew from the trial because of adverse events, compared with 1 in the placebo group. A total of 12 patients in the CBD group and 1 in the placebo group had elevated aminotransferase levels; they were all also taking valproate. Of the 9 patients who continued taking CBD (3 patients withdrew from the trial), enzyme levels returned to normal during the trial, suggesting transient metabolic stress on the liver. Differences in unpalability between the active treatment and placebo could have affected blinding in a small number of patients. The length of the trial did not allow for the assessment of the potential development of tolerance so additional data are needed to determine the long-term efficacy and safety of CBD for the Dravet syndrome [576].

A randomized, double-blind, placebo-controlled clinical trial was conducted to investigate the efficacy of Epidiolex® as add-on therapy for drop seizures in patients with treatment-resistant Lennox-Gastaut syndrome [577]. After a 4-week baseline period, 171 eligible patients (aged 2-55 years) were randomized (1:1) to either receive 20 mg/kg CBD daily (n=86) or placebo (n=85) as 2 equivalent doses (morning and evening) for 14 weeks (2 weeks of dose escalation and 12 weeks of dose maintenance). The median percentage reduction in monthly drop seizure frequency from baseline (primary endpoint) was 43.9% [interquartile range (IQR) -69.6 to -1.9] in the CBD group and 21.8% (IQR -45.7 to 1.7) in the placebo group. The estimated median difference between the treatment groups was -17.21 (95% CI -30.32 to -4.09; p = 0.0135) during the 14-week treatment period. The treatment effect of CBD on the primary endpoint was established during the first 4 weeks of the maintenance period and was maintained during the full treatment period. In the CBD group, 38 patients (44%) had a reduction in drop seizure frequency of ≥50% from baseline during the treatment period compared with 20 patients (24%) in the placebo group (OR 2.57, 95% CI 1.33-4.97; p = 0.0043). There were 3 patients in the CBD group who were free of drop seizures throughout the 12-week maintenance period; their monthly frequency of drop seizures at baseline was in the lower range of 15.6 to 99.2. During the treatment period, CBD also significantly decreased the estimated median difference in the monthly frequency of total seizures [-21.1 (95% CI -33.3 to -9.4; p = 0.0005)] and non-drop seizures [-26.1 (95% CI -46.1 to -8.3; p = 0.0044)] compared to placebo. This suggested that add-on CBD may have broad spectrum effects on seizure reduction. Common adverse events (occurring in ≥10% of patients) in the CBD group were diarrhea (19%), somnolence (15%), pyrexia (13%), decreased appetite (13%) and vomiting (10%). Most of the adverse events were mild or moderate in severity (78% in the CBD group) and resolved by the end of the trial (61%). Adverse events led to study withdrawal in 12 patients (14%) in the CBD group and 1 (1%) patient in the placebo group. Of the 20 patients in the CBD group who had elevations in ALT or AST (>3 times upper limit of normal), irrespective of whether they were reported as adverse events, 16 were also taking valproate. The most common serious treatment-related adverse events (occurring in >3% of patients) were collectively reported in 4 patients in the CBD group and comprised increased ALT (n=4), AST (n=4) and γ-glutamyltransferase (n=3) concentrations. No patients met standard criteria for drug-induced severe liver injury (Hy's law). Overall, this trial demonstrated that add-on CBD was efficacious for the treatment of patients with drop seizures associated with Lennox-Gastaut syndrome and was generally well tolerated. However, only a single dose of CBD was tested in this trial; dose-response effects will be assessed further in another study (GWPCARE3; ClinicalTrials.gov**,** number NCT02224560). Further assessment of the long-term efficacy and safety of CBD is being carried out in the ongoing open-label extension of this trial and will also be done using real-world data, once available [577].

A double-blind, placebo-controlled clinical trial was conducted to determine the efficacy and safety of Epidiolex® (CBD) as an adjunct to conventional antiepileptic drugs to treat drop seizures in patients with Lennox-Gastaut syndrome, a severe developmental epileptic encephalopathy [760]. A total of 225 patients (aged 2-55) with Lennox-Gastaut syndrome and ≥2 drop seizures per week during a 28-day baseline period were randomly assigned to receive 20 mg/kg CBD (n=76), 10 mg/kg CBD (n=73) or placebo (n=76) as 2 equally divided doses daily for 14 weeks (2 weeks dose escalation followed by 12 weeks of maintenance). The median percent reduction from baseline in the frequency of drop seizures per 28 days during the treatment period (primary outcome) was 41.9% ($p = 0.005$), 37.2% ($p = 0.002$) and 17.2% in the 20 mg/kg CBD, 10 mg/kg CBD and placebo groups, respectively. During the treatment period, a total of 30 patients (39%) in the 20 mg/kg CBD group (OR 3.8; 95% CI 1.75-8.47; $p < 0.001$), 26 patients (36%) in the 10 mg/kg CBD group (OR 3.27; 95% CI 1.46-7.26; $p = 0.003$) and 11 patients (14%) in the placebo group had ≥50% reduction from their baseline in drop-seizure frequency. The percentage of patients who had ≥75% reduction from baseline in drop-seizure frequency was higher in the 20 mg/kg CBD group (25%) and the 10 mg/kg CBD group (11%) than in the placebo group (3%). No patients were free from drop seizures during the entire treatment period (day 1 onward); however, 5 patients (7%), 3 patients (4%) and 1 patient (1%) in the 20 mg/kg CBD, 10 mg/kg CBD and placebo groups, respectively, were free from drop seizures during the entire maintenance phase (day 15 onward). The median percent reduction from baseline in the frequency of all seizures per 28 days during the treatment period was 38.4% ($p = 0.009$), 36.4% ($p = 0.002$) and 18.5% in the 20 mg/kg CBD, 10 mg/kg CBD and placebo groups, respectively. Adverse events were reported in 72-94% of patients, the majority of which (89%) were considered mild or moderate in severity. The most common adverse events with CBD were somnolence (n=14-25), decreased appetite (n=11-21), and diarrhea (n=7-12); these events occurred more frequently in the 20 mg/kg CBD group. Serious adverse events (n=26 vs. n=7) and trial withdrawal (n=7 vs. n=1) were more common in the CBD groups than in the placebo group. Serious adverse events considered related to CBD occurred in 7 patients (1 patient had multiple events) and included elevated aspartate aminotransferase concentration (n=2), elevated alanine aminotransferase concentration (n=1), elevatedγ-glutamyltransferase concentration (n=1), somnolence (n=1), increased seizures during weaning (n=1), non-convulsive status epilepticus (n=1), lethargy (n=1), constipation (n=1) and worsening chronic cholecystitis (n=1). Maximum elevations in aspartate aminotransferase or alanine aminotransferase concentrations 3.2-12.2 times the upper limit of normal were the most common adverse events leading to trial withdrawal in the CBD groups (n=5). Elevations in aminotransferase concentrations >3 times the upper limit of normal occurred more frequently in patients receiving 20 mg/kg CBD (n=11) than in those receiving 10 mg/kg CBD (n=3). In most of these cases (n=11, 79%), patients were receiving valproate concomitantly. No patient met the criteria for severe drug-induced liver injury (DILI). The majority of these cases (n=9) resolved after the dose of CBD was tapered, discontinued or the dose of another antiepileptic drug was reduced [760].

A recent systematic review of 36 studies (30 observational; 6 RCTs) regarding cannabinoids' impact as an adjunctive treatment in epileptic patients (mean age 16 years) suggested that pharmaceutical-grade CBD was more effective than placebo at reducing seizure frequency by 50%, achieving complete seizure freedom (RR 6.17, 95% CI 1.50-25.32), and improving quality of life (RR 1.73, 95% CI 1.33 - 2.26) compared to placebo. Adverse effects from pharmaceutical-grade CBD included drowsiness, fatigue, diarrhea, changes in appetite, and ataxia. These findings were specific to individuals with rare and serious forms of drug-resistant epilepsy; hence, the results cannot be generalized to adult/older population or to those with less severe epilepsy syndromes [761].

4.7 Pain

It is now well established that the ECS plays an important role in the modulation of nociceptive and pain states. Key in these roles is the specific positioning of the endocannabinoid signaling machinery at neuronal synapses in pain processing pathways at supraspinal, spinal, and peripheral levels [24, 762-764].

Role of CB_1 and CB_2 receptors

The CB_1 and CB_2 receptors play important roles in nociception and pain. Structures involved in transmission and processing of nociceptive signals such as the nociceptors, the dorsal horn of the spinal cord, the thalamus, the periaqueductal grey matter, the amygdala and the rostroventromedial medulla show a moderate to high level of CB_1 receptor expression [765]. In various animal models of chronic pain, both CB_1 and CB_2 receptor mRNA and protein levels in the CNS are upregulated [765]. Selective deletion of the CB_1 receptor in mice appears to greatly attenuate the anti-nociceptive efficacy of cannabinoids in animal models of acute and chronic pain, suggesting an essential role for this receptor in modulating nociception and pain [762, 766]. At peripheral and central terminals of nociceptive sensory nerves, CB_1 receptors gate the transduction of peripheral noxious stimuli into central neuronal pain signals [762, 767], while in the spinal cord, CB_1 receptors act to reduce or enhance propagation of pain signals to the brain [762, 768-770]. At the neuronal circuit level, the end result of CB_1 receptor activity can be either excitatory or inhibitory depending on the identity of the presynaptic cell and its location within the neural network [762]. In higher brain regions tasked with processing of nociceptive input such as the periaqueductal grey matter and the rostroventromedial medulla, the CB_1 receptors can initiate descending inhibition or block descending facilitation to the spinal cord nociceptive circuitry [762, 771-776]. Most importantly to the subject of pain, CB_1 receptors are highly expressed in frontal-limbic pathways in the brain, which play a key role in the affective/emotional aspects of pain in humans [762, 772, 777]. CB_2 receptors appear to also play an important role in pain signaling, especially in the development of chronic pain states, by inhibiting the release of pro-inflammatory and pro-nociceptive mediators thereby attenuating the inflammatory and hyperalgesic responses [762, 778]. In this respect, the strategic localization of CB_2 receptors on a variety of immune cells (macrophages, lymphocytes, and mast cells in the periphery), astrocytes and microglia in the CNS (i.e. the spinal cord) is essential to the roles of the CB_2 receptors in modulating pain states.

Role of endocannabinoids, anandamide and 2-AG

Endocannabinoids such as anandamide and 2-AG have been shown to have analgesic or anti-nociceptive effects at peripheral, spinal, and central levels, mainly by virtue of their ability to stimulate the activity of the cannabinoid receptors, although other receptors (i.e. TRPV1) are also likely involved [779]. Peripheral inhibition of FAAH and MAGL enzymes (which hydrolyze anandamide and 2-AG respectively) and the resulting increase in the respective synaptic levels of anandamide and 2-AG has been shown to reduce nociception in animal models of acute and chronic pain [762, 767, 780-791]. Meanwhile, the arachidonoyl moiety of anandamide and 2-AG makes these endocannabinoids susceptible to metabolism by eicosanoid biosynthetic enzymes such as COXs, lipo-oxygenases (LOXs), and CYPs with the subsequent generation of known or potential *pro*-nociceptive prostamide endocannabinoid metabolites [762, 792, 793]. Therefore, the upregulation of COX-2 expression in chronic pain states may promote the additional production of these *pro*-nociceptive metabolites both peripherally and centrally thus contributing to nociception and pain [765].

Considerations and caveats

Animal vs. human studies

Pre-clinical studies in animals predict that cannabinoids should relieve both acute and chronic pain in humans. 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 in humans [794-796]. A number of possible explanations can exist to account for discrepancies in findings 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 [23, 797]. This pharmacological overlap can make it difficult to distinguish between cannabinoid-associated anti-nociceptive effects and behavioural effects [23, 797].

Experimental models of acute pain vs. chronic pain

Translation of research findings from human experimental models of pain (i.e. acute pain) to clinical (chronic) pain is also complex and not straightforward [268]. In contrast to acute pain, chronic pain is a complex condition that involves interaction between sensory, affective, and cognitive components [268]. Furthermore, unlike acute pain, chronic pain is considered a disease and generally originates from prolonged acute pain that is not managed in a timely or effective manner [798]. Chronic pain also appears to involve distinct spatiotemporal neuronal mechanisms which differ from those recruited during acute, experimental pain [799]; chronic pain involves altered neural transmission and long-term plasticity changes in the peripheral and CNS which generate and maintain the chronic pain state [798, 799]. 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 [268].

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) [800, 801]. Of note, in one randomized, placebo-controlled clinical study of vapourized cannabis for painful diabetic neuropathy, the placebo effect was as high as 56% for euphoria and as high as 37.5% for somnolence out of a maximum 100% euphoria and 73.3% somnolence responses (observed with the highest THC dose condition at 7% THC) [599]. Emerging evidence also suggests an important role for the ECS in *mediating* placebo analgesia [802-804]. These findings highlight the complexities of studying the true analgesic potential of cannabinoids and underscore the importance of including a properly designed placebo control when studying the analgesic potential of cannabinoids.

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 MS) 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 [612]. 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 enriched for patients that responded favourably to the treatment and conversely, eliminated subjects who would have either responded poorly to cannabinoids or who would have had greater chances of experiencing adverse effects [55]. Therefore, 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 [55, 612]. There is also some evidence from pre-clinical and clinical studies that suggests sex-dependent effects on cannabinoid and cannabis-induced analgesia (see **Section 2.5**, *Sex-dependent effects*, for more information) [563, 805-807].

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 for the treatment of pain [23, 55, 57, 797]. The well-known psychotropic and somatic side-effects associated with the use of THC-enriched 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 ECS (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 [23, 57].

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.

4.7.1 Acute pain

- ***Pre-clinical studies suggest that certain cannabinoids can block the response to experimentally-induced acute pain in animal models.***
- ***The results from clinical studies with smoked cannabis, oral THC, cannabis extract, and nabilone in experimentally-induced acute pain in healthy human volunteers are limited and mixed and suggest a dose-dependent effect in some cases, with lower doses of THC having an analgesic effect and higher doses having a hyperalgesic effect.***
- ***Clinical studies of certain cannabinoids (nabilone, oral THC, levonontradol, AZD1940, GW842166) for post-operative pain suggest a lack of efficacy.***

4.7.1.1 Experimentally-induced acute pain

Pre-clinical studies

Cannabinergic modulation of neuronal circuits in the brain and spinal cord can inhibit nociceptive processing [808-811] and 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 [23, 797]).

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 Δ^9-THC *available in the cigarette*) in response to transcutaneous electrical stimulation [812]. 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 Δ^9-THC *available in the cigarette*) increased pain tolerance to a pressure stimulus in both healthy cannabis-naïve and cannabis-experienced subjects compared to placebo [813]. Another study employing healthy cannabis smokers reported that smoking cannabis cigarettes (containing 3.55% Δ^9-THC, or approximately 62 mg Δ^9-THC *available in the cigarette*) was associated with a mild, dose-dependent, anti-nociceptive effect to a thermal heat stimulus [273]. 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 [268]. 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); the low dose (2% Δ^9-THC) had no effect whereas a high dose (8% Δ^9-THC) 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) [272]. 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) [267]. 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) [268].

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 [814]. 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 analgesia could have been attributed to the single-dose administration of the cannabinoid; a gradual dose escalation could have potentially revealed an effect.

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 [600]. 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 to 6 h after dosing, reaching a maximum between 4 and 6 h after administration.

4.7.1.2 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 [270, 815]. To date, there are eight published reports and a systematic review on the use of cannabinoids in post-operative pain [269-271, 274, 816 269-271, 274, 796, 816-819]. The conclusions from the systematic review was that the studied cannabinoids (THC, nabilone, or an oral cannabis extract containing a 2 : 1 ratio of THC to CBD, levonontradol, AZD1940, GW842166) were not ideally suited for the management of acute post-operative pain because they were either only moderately effective [270, 274], less effective than placebo [817], not different from placebo [271, 796, 816, 818 271, 796], or even anti-analgesic at high doses [269].

4.7.2 Chronic pain

Acute pain that is poorly managed can lead to chronic pain [820, 821]. 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 QoL [822]. The International Association for the Study of Pain defines pain as chronic if it persists beyond the normal tissue healing time of three to six months [823]. Furthermore, chronic pain is associated with an abnormal state of responsiveness or increased gain of the nociceptive pathways in the CNS (referred to as "central sensitization"), as well as with alterations in cognitive functioning [823]. The information below summarizes pre-clinical studies carried out in animal models of chronic pain, and clinical studies in human subjects administered an experimental stimulus mimicking chronic pain or in patients suffering from chronic pain of various etiologies.

4.7.2.1 Experimentally-induced inflammatory and chronic neuropathic pain

- ***Endocannabinoids, THC, CBD, nabilone and certain synthetic cannabinoids have all been identified as having an anti-nociceptive effect in animal models of chronic pain (inflammatory and neuropathic).***

The anti-nociceptive efficacy of cannabinoids has been unequivocally demonstrated in several different animal models of inflammatory and neuropathic pain (reviewed in [765, 779, 824, 825]}}). In addition, the findings from these studies suggest that modulation of the ECS through administration of specific cannabinoid receptor agonists, or by elevation of endocannabinoid levels, suppresses hyperalgesia and allodynia induced by diverse neuropathic states (reviewed in [765, 779, 825]). 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 in this pain state (reviewed in [23, 797, 825]).

With respect to CBD, chronic oral administration of CBD effectively decreased hyperalgesia in a rat model of inflammatory pain [826]. One study suggested that a medium or a high dose of CBD attenuated 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 was little, if any, restorative effect if CBD was administered at a later time point [827]. In contrast, the same study showed that 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. 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. Xiong et al. (2012) reported that systemic and intrathecal administration of CBD potentiated glycine currents, through α3 glycine receptors, in dorsal horn neurons in rat spinal cord slices and also attenuated chronic inflammatory and neuropathic pain *in vivo* [828].

4.7.2.2 Neuropathic pain and chronic non-cancer pain in humans

- ***A few studies that have used experimental methods having predictive validity for pharmacotherapies used to alleviate chronic pain, have reported an analgesic effect of smoked cannabis.***
- ***Furthermore, there is more consistent evidence of the efficacy of cannabinoids (smoked/vapourized cannabis, nabiximols, dronabinol) in treating chronic pain of various etiologies, especially in cases where conventional treatments have been tried and have failed.***

Clinical studies with cannabinoids

A systematic review and meta-analysis of 28 RCTs (N = 2 454 participants) for chronic pain (including smoked cannabis, nabiximols, dronabinol) reported that there was moderate quality evidence of efficacy to support the use of cannabinoids to treat chronic pain of various etiologies mostly reducing central or peripheral neuropathic pain in individuals already receiving analgesic drugs [179]. The working definition of chronic pain included neuropathic (central/peripheral), cancer pain, diabetic peripheral neuropathy, fibromyalgia, HIV-associated sensory neuropathy, refractory pain due to MS or other neurological condition, rheumatoid arthritis (RA), non-cancer pain (nociceptive/neuropathic), central pain, musculoskeletal pain and chemotherapy-induced pain. The average number of patients who reported a reduction in pain of at least 30% was greater with cannabinoids vs. placebo (OR = 1.41), although for smoked cannabis the effect was greater (OR = 3.43). Side effects appeared to be comparable to existing treatments and included dizziness/lightheadedness, nausea, fatigue, somnolence, euphoria, vomiting, disorientation, drowsiness, confusion, loss of balance, hallucinations, sedation, ataxia, a feeling of intoxication, xerostomia, dysgeusia, and hunger [172, 176, 829, 830]. However, these adverse 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 smoked/vapourized cannabis and cannabinoids (THC, nabilone, dronabinol and nabiximols) to treat neuropathic and chronic non-cancer pain.

Clinical studies with smoked or vapourized cannabis

A within-subject, randomized, placebo-controlled, double-dummy, double-blind clinical study compared the acute therapeutic analgesic potential of two potencies of smoked cannabis (1.98% and 3.56% THC, 800 mg cigarettes with 16 mg and 28 mg THC respectively) to two doses of dronabinol (10 and 20 mg) in response to an experimental pain stimulus (i.e. cold pressor test) that has predictive validity for pharmacotherapies used to treat chronic pain [831]. The study found that both cannabis and dronabinol produced analgesic effects in this model and there were also no significant differences between dronabinol and smoked cannabis in measures of pain sensitivity (i.e. latency to first feel pain). However, in terms of pain tolerance, low potency smoked cannabis (1.98% THC) and both low and high dronabinol doses increased the latency to report pain relative to placebo. Both strengths of cannabis and the high dronabinol dose (20 mg) decreased subjective ratings of pain intensity and bothersomeness of the cold-pressor test compared to placebo although these decreases were greater after cannabis relative to dronabinol. Both cannabis strengths and the high dronabinol dose increased subjective ratings of "high" and "good drug effect" relative to placebo, and both cannabis strengths (but not the low dronabinol dose) increased ratings of "stimulated" relative to placebo. Lastly, both strengths of cannabis and the high dronabinol dose increased ratings of "marijuana strength", "liking", and "willingness to take again". There did not appear to be any sex-dependent differences in terms of baseline pain measures, analgesic, subjective, or physiological effects across all cannabis or dronabinol conditions. Overall, dronabinol decreased pain sensitivity and increased pain tolerance and these effects peaked later and lasted longer compared to smoked cannabis, while smoked cannabis produced a greater attenuation of subjective ratings of pain intensity compared to dronabinol. Peak subjective ratings of dronabinol's drug effects occurred significantly earlier than decreases in pain sensitivity and increases in pain tolerance (60 min vs. 4 h). Limitations of this study include a potentially biased study population that consisted of daily cannabis users as well as the experimental nature of the pain stimulus in subjects not normally experiencing pain.

A retrospective analysis that compared the analgesic, subjective, and physiological effects of smoked cannabis (3.56 or 5.60% THC, 800 mg cigarettes with 28 mg and 45 mg THC respectively) in 21 men and 21 women under double-blind, placebo-controlled conditions showed that among men, cannabis significantly decreased pain sensitivity in the cold pressor test compared to placebo, while in women active cannabis failed to decrease pain sensitivity relative to placebo [807]. Active cannabis increased pain tolerance in both men and women immediately after smoking as well as increased subjective ratings associated with abuse liability ("take again", "liking", "good drug effect"), drug strength, and "high" relative to placebo. Ratings of "high" varied as a function of sex, with men exhibiting elevated ratings throughout the session relative to women. Men also exhibited greater increases in heart rate after smoking cannabis compared to women. Study subjects smoked cannabis daily or near-daily, and smoked on average 7 to 10 cannabis cigarettes/day.

In a 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 [195]. The 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. 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.

In another randomized, double-blind, placebo-controlled, cross-over study of cannabis-experienced patients suffering from chronic neuropathic pain of various etiologies (complex regional pain syndrome (CRPS), central neuropathic pain from SCI or MS, 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 [222]. No analgesic effect was observed in tests of experimentally-induced pain (tactile or heat stimuli) in these participants. Patients were taking other pain control medications during the trial such as opioids, anti-depressants, NSAIDs, 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.

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 [281]. 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, NSAIDs, 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.

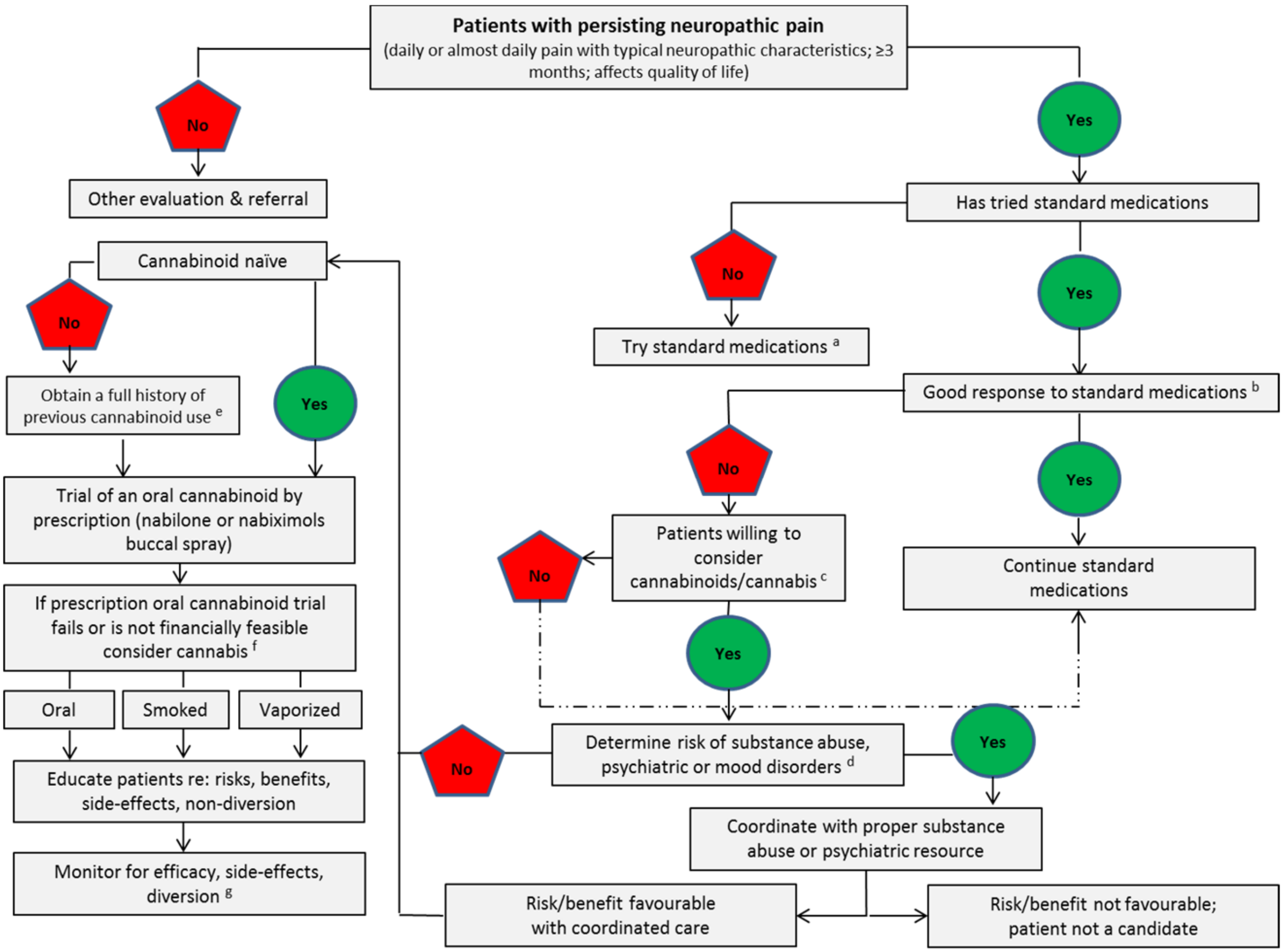
A randomized, double-blind, placebo-controlled, four-period, crossover clinical study of smoked cannabis for chronic neuropathic pain caused by trauma or surgery and refractory to conventional therapies reported that compared to placebo, a single smoked inhalation of 25 mg of cannabis containing 9.4% 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 [59]. 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 NSAIDs. 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 examined the effects of vapourized cannabis on the pharmacokinetics, subjective effects, pain ratings and safety of orally-administered opioids in patients suffering from chronic pain (musculoskeletal, post-traumatic, arthritic, peripheral neuropathy, cancer, fibromyalgia, MS, sickle cell disease, and thoracic outlet syndrome) [280]. The study reported that inhalation of vapourized cannabis (900 mg, 3.56% Δ^9-THC), three times per day for five days, was associated with a statistically significant decrease in pain (-27%, CI = 9 – 46). Subjects were on stable doses of sustained-release morphine sulfate or oxycodone, and had prior experience with smoking cannabis. There was a statistically significant decrease in the 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 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 (SCI, CRPS type I, causalgia-CRPS type II, diabetic neuropathy, MS, post-herpetic neuralgia, idiopathic peripheral neuropathy, brachial plexopathy, lumbosacral radiculopathy, and post-stroke neuropathy) reported that inhalation of vapourized cannabis (800 mg 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 [598]. 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 (10s), and finally exhale and wait before repeating the inhalation cycle (40s). 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 (four to eight puffs, flexible dosing, 2 h after first inhalation), was associated with continued analgesia lasting another 2 h. 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 low-dose vs. placebo, 2.9 for the medium-dose vs. placebo, and 25 for the medium- vs. the low-dose. 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 NSAIDs). Cannabis treatment was associated with a small impairment of certain cognitive functions, with the greatest effects seen in domains of learning and memory. 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.

A review of the use of smoked cannabis for the treatment of neuropathic pain suggested that the efficacy of smoked cannabis (NNT = 3.6, for a 30% reduction in pain) was comparable to that of traditional therapeutic agents (e.g. gabapentin, NNT = 3.8), slightly less than that observed with tricyclic antidepressants (NNT = 2.2), but better than lamotrigine (NNT = 5.4) and selective serotonin reuptake inhibitors (NNT = 6.7) [832]. The author reports that the concentrations of THC in the smoked cannabis ranged between 2 and 9% with an average concentration of 4% yielding good efficacy. Furthermore, the author suggests that cannabis may present a reasonable alternative or adjunctive treatment for patients with severe, refractory peripheral neuropathy who have tried other therapeutic avenues without satisfactory results. This review, along with another more recent review [275] provide a useful clinical algorithm for determining if a patient would be a candidate for treatment with cannabis for peripheral neuropathic pain (see **Figure 3**).

Figure 3. A Possible Clinical Algorithm for Physicians Considering Supporting Therapeutic Use of Cannabis for a Patient with Chronic, Intractable Neuropathic Pain. Figure adapted from [275, 832]



Legend:

[a] Standard medications include antidepressants, anticonvulsants, opioids, nonsteroidal anti-inflammatory drugs.

[b] At least 30% reduction in pain intensity.

[c] Consider past experience with cannabis or cannabinoids, potential for side effects or history of side effects, willingness to smoke/vapourize/ingest orally.

[d] Determine substance abuse history; history of psychiatric or mood disorders. If yes or at high risk for substance abuse, proceed with caution and close observation (see **Sections 2.4**, **5.0**, and **6.0**); coordinate with substance abuse treatment programs. If there is a history or risk of psychiatric disease (schizophrenia) or bipolar disorder see **Section 7.7.3** and consult with a psychiatric specialist before proceeding.

[e] Specific cannabinoid, dose, route of administration; symptoms treated and outcome; adverse effects.

[f] Discuss the fact that there are not yet clear guidelines regarding efficacy, doses and toxicity; raise awareness of oral and vapourized routes of cannabis administration; refer patient to Health Canada website and documents regarding access to cannabis product(s); follow the usual clinical guideline to start low and titrate dose slowly.

[g] Efficacy should aim for at least 30% decrease in pain intensity.

A single-dose, open-label, clinical trial of patients with neuropathic pain and using very low doses of THC (from vapourized cannabis) reported a statistically significant improvement in neuropathic pain with minimal adverse effects [58]. In this clinical study, 10 patients suffering from neuropathic pain of any type (SCI, CRPS, lumbosacral radiculopathy, pelvic neuropathic pain) of at least three months duration and on a stable analgesic regimen for at least 60 days (e.g. opioids, antidepressants, anticonvulsants, benzodiazepines, steroids, NSAIDs, cannabis) were administered a vapourized dose of 3 mg of THC (available in the device; ~ 1.5 mg THC actually delivered) resulting from vapourization of 15 mg of dried cannabis containing 20% THC. THC administration was associated with a statistically significant reduction in baseline VAS pain intensity of 3.4 points (i.e. a 45% reduction in pain) within 20 min of inhalation with a return to baseline within 90 min. Adverse effects were minimal but included lightheadedness for 10 min after inhalation which lasted approximately 30 min and then fully resolved. Subjects reported using between 2 and 40 g of cannabis per month (i.e. 0.067 g per day and 1.3 g per day). THC was detected in blood within 1 min following inhalation and reached a maximum within 3 min at a mean THC concentration of 38 ng/ml.

A Canadian multi-centre, prospective, cohort safety study of patients using cannabis as part of their pain management regimen for chronic non-cancer pain reported that cannabis use was not associated with an increase in the frequency of serious adverse events vs. controls, but was associated with an increase in the frequency of non-serious adverse events [216]. In this study, 216 patients with chronic non-cancer pain (nociceptive, neuropathic, or both) using cannabis and 215 control patients with chronic pain with no cannabis use were followed for a period of one year and evaluated for frequency and type of adverse effects associated with the use of a standardized herbal cannabis product (CanniMed 12.5% THC, <0.5% CBD). A significant proportion of study subjects were taking opioids, anti-depressants or anti-convulsants. Almost one third of study subjects who reported smoking cannabis at least once reported consuming it exclusively by smoking, 44% reported smoking and oral ingestion, 14% reported vapourizing, smoking or ingesting cannabis orally, and slightly less than 4% reported only smoking or vapourizing. Secondary objectives were to examine the effects of cannabis use on pulmonary and neurocognitive function and to explore the effectiveness of cannabis for chronic non-cancer pain, including pain intensity and QoL. For the primary outcome, the total number of serious adverse events was similar between the cannabis group and the control group and none of the serious adverse events were considered to be either “certainly” or “very likely” related to the cannabis provided by the investigators. One serious adverse event (convulsion) was considered to be “probably/likely” related to the study cannabis. Patients in the cannabis-treatment group experienced a median of three events per subject (vs. a median of two events per subject among controls). The incidence rate of adverse events in the cannabis treatment group was 4.61 events/person-year and was significantly higher than in the control group where the incidence rate was 2.85 events/person-year. The most common adverse event categories in the cannabis-treatment group were nervous system (20%), GI (13.4%), and respiratory disorders (12.6%) and the rate of nervous system disorders, respiratory disorders, infections, and psychiatric disorders was significantly higher in the cannabis group than in the control group. Furthermore, mild (51%) and moderate (48%) events were more common than severe ones (10%) in the cannabis-treatment group. Somnolence (0.6%), amnesia (0.5%), cough (0.5%), nausea (0.5%), dizziness (0.4%), euphoric mood (0.4%), hyperhidrosis (0.2%), and paranoia (0.2%) were assessed as being “certainly/very likely” related to treatment with cannabis. Increasing the daily dose of cannabis was not associated with a higher risk of serious or non-serious adverse events, although the recommended maximum daily amount of cannabis was set at 5 g per day (the median daily cannabis dose was 2.5 grams per day). With respect to secondary outcomes, no difference in neurocognitive function was found between cannabis users and controls, after one year of treatment and after controlling for multiple potential confounders. No significant changes were noted in certain pulmonary function tests (Slow Vital Capacity, Functional Residual Capacity, Total Lung Capacity) over the course of the study period, although reductions were noted in residual volume, forced expiratory volume in one second (FEV_1) and in the FEV_1/forced vital capacity (FVC) ratio (0.78% decrease). No changes were observed in liver, renal or endocrine functions. In terms of efficacy for pain, compared to baseline, there was a significant reduction in average pain intensity in the cannabis-treatment group but not in the control (difference = 1.10). Notably, patients using cannabis had higher baseline pain and disability than controls. While there was a significant improvement from baseline pain intensity in both the control and cannabis-treatment groups, greater improvement of physical function was observed in the cannabis group vs. control. Lastly, the sensory component of pain and total symptom distress score (Edmonton Symptom Assessment System) as well as the total mood disturbance scale of the Profile of Mood States all showed improvement in the cannabis group vs. control. Limitations of the study included relatively small sample size and short follow-up time which prevented the identification of rare serious adverse events, a significant drop-out rate attributable to adverse events (especially among cannabis naïve and former users), perceived lack of efficacy, and/or dislike of the study product. The majority (66%) of individuals in the cannabis group was composed of experienced cannabis users and the authors of the study suggest that a higher rate of adverse events for cannabis may have been observed if only new cannabis users had been included. Therefore, the study findings regarding safety of cannabis use for chronic non-cancer pain cannot be generalized to patients who are cannabis naïve. Lastly, the study was not a RCT and allocation was not blinded, therefore improvements in secondary efficacy measures should be interpreted with caution.

A meta-analysis of randomized, double-blind, placebo-controlled trials of smoked/vapourized cannabis for neuropathic pain reported that inhaled cannabis resulted in short-term reductions in chronic neuropathic pain for one in every five to six patients treated (NNT = 5.6) [833]. Furthermore, the study results suggested that inhaled cannabis may be as potent as gabapentin (NNT = 5.9). In this study, one hundred and seventy-eight middle-aged participants with painful neuropathy of at least three months' duration were enrolled in the five North American RCTs examined — two RCTs recruited only HIV+ individuals with HIV-related chronic painful neuropathy, while the remaining three RCTs recruited patients with neuropathy secondary to trauma, SCI, diabetes mellitus and CRPS. No studies investigated outcomes beyond two weeks. Therapeutic effects appeared to increase with increasing THC content. Study withdrawals due to adverse effects were rare. Subjective side effects included mild anxiety, disorientation, difficulty concentrating, headache, dry eyes, burning sensation, dizziness, and numbness. Psychoactive effects (e.g. "feeling high") increased in frequency with increasing dose. Limitations of this study are mainly reflective of the limitations associated with the original studies (i.e. small number of available studies, small number of participants, shortcomings in allocation concealment, and attrition). The meta-analysis could not draw any conclusions regarding the long-term efficacy or safety of inhaled cannabis for chronic neuropathic pain, as the original studies did not extend past a maximum two-week period.

A randomized, double-blind, placebo-controlled, single-dose, cross over clinical trial of low, medium and high-dose vapourized cannabis in 16 patients with painful diabetic peripheral neuropathy measuring short-term efficacy and tolerability reported a statistically significant difference in spontaneous pain scores between doses and a statistically significant negative effect of the high dose on some neuropsychological measures [599]. Study participants had diabetes mellitus type I or II and had at least a six-month history of painful diabetic peripheral neuropathy. Subjects participated in four sessions, separated by two weeks and were exposed to placebo, low (1% THC, <1% CBD, 400 mg total plant material), medium (4% THC, <1% CBD, 400 mg total plant material) and high (7% THC, <1% CBD, 400 mg total plant material) doses of THC; actual doses of THC available for inhalation were estimated at 0, 4, 16, or 28 mg THC per dosing session. Baseline measurements of spontaneous pain, evoked pain and cognitive testing were performed. There was a reported statistically significant difference in *spontaneous* pain scores between doses, with the average pain intensity scores with the low, medium and high doses being significantly different from the placebo, and the average pain score with the high dose being significantly different from the average pain score in the medium, low dose and placebo; no statistically significant difference in average pain intensity was noted between the medium and low dose. There was a statistically significant reduction in mean *evoked* pain scores between the placebo and high dose, between the low and high dose, and between the medium and high dose of cannabis. On average, the lowest minimum pain score was achieved with the high dose (7% THC), and the highest minimum pain score was seen with the placebo dose. While results showed a statistically significant reduction in *both* spontaneous and evoked pain between doses, comparison of the proportions of participants who achieved at least 30% reduction in *spontaneous* and *evoked* pain scores was not statistically significant between the different doses. Performance on selected neurocognitive tests (attention/working memory) showed statistically significant differences between doses, with some impairments lasting up to 120 min post-administration. There was a dose-dependent effect in subjective "highness" score that dissipated after 4 h. Furthermore, the study findings suggested a correlation between subjective "highness" score and spontaneous pain score, with every 1-point increase in "highness" score associated with a pain score decrease of 0.32 points. Euphoria was noted in 100% of individuals at the highest dose (7% THC), and there was a statistically significant difference in euphoria between the high dose and placebo and the medium dose and placebo. Somnolence was noted in 73% of individuals at the high dose and was only statistically significant for the high dose vs. placebo. Interestingly, 56% of individuals reported euphoria with the placebo dose, suggesting a high expectancy rate. Limitations of the study included small sample size, underpowering, brief duration, limited neuropsychiatric testing, and potential unblinding.

A systematic review of RCTs examining cannabinoids (nabilone, oral mucosal cannabis spray, oral cannabis extract, smoked or vapourized cannabis, and FAAH inhibitors) in the treatment of chronic non-cancer pain was conducted according to Preferred Reporting Items for Sytematic Reviews and Meta-Analyses (PRISMA) guidelines on health care outcomes and showed that the majority of the trials demonstrated a significant analgesic effect as well as improvements in secondary outcomes (e.g. sleep, muscle stiffness, spasticity) [176]. Frequent adverse effects, likely caused by cannabis, included drowsiness, fatigue, dizziness, dry mouth, nausea and cognitive effects that were generally mild to moderate in severity and generally well tolerated. Serious adverse effects included urinary tract infection, head injury, and interstitial lung disease (oral cannabis extract), delirium (nabilone), and suicidal ideation and disorientation (oral mucosal cannabis spray). Limitations of the findings relate mainly to the short duration and small sample sizes of the included trials and the modest effect sizes. RCTs of longer duration and with a larger sample size are needed to confirm efficacy signals reported by the smaller "proof of concept" studies, and for longer term monitoring of patients to assess long-term safety.

Another systematic review of six RCTs (N = 226 patients) of smoked or vapourized cannabis for chronic non-cancer pain reported evidence for the use of low-dose cannabis in refractory neuropathic pain in conjunction with traditional analgesics [172]. Five out of the six included RCTs were considered high quality (using the Jadad scale). Two-hundred and twenty-six adults (mean age 45 to 50) with chronic neuropathic pain (HIV-associated neuropathy, post-traumatic neuropathy, mixed neuropathy) were included in the analysis. All included trials excluded patients with a history of psychotic disorders, previous history of cannabis abuse or dependence. Four of the five trials that allowed patients to continue using opioids, anticonvulsants, and anti-depressants reported that more than 50% of subjects used concomitant opioids. Dose of THC ranged from about 1% to 9.4% (by dry weight) with the total daily THC amount delivered ranging from 1.9 mg/day to a maximum of 34 mg/day. The two trials open to cannabis-naïve subjects reported dropouts or withdrawals associated with potential adverse effects of smoked cannabis (e.g. psychosis, persistent cough, feeling "high", dizziness, fatigue) with the remaining reasons for dropouts unrelated to adverse effects. All studies reported a statistically significant analgesic effect. Clinically meaningful analgesic effect (> 30% improvement in pain relief) was reported in only three of the included studies. Adverse effects included mainly neurologic or psychiatric events (e.g. headache, sedation, euphoria, dysphoria, poor concentration, attention and memory) and the incidence of these adverse effects appeared to increase in frequency with increasing dose of THC. The authors conclude that the short-term adverse cognitive effects reported in the included RCTs were similar to those experienced with opioids and suggest the same precautions used with opioids should be applied to cannabis. The authors suggest that low-dose THC (< 34 mg THC/day) is associated with an improvement in refractory neuropathic pain of moderate severity in adults using concurrent analgesics. Generalizability of the results in chronic non-cancer pain is limited by quality of the studies, small sample sizes, short duration, and dose and dose scheduling variability.

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 [822]. 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 NSAIDs, 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 ≥ 30% reduction in pain from baseline to end point, and 31% of subjects in the nabilone group reporting a ≥ 50% reduction in pain from baseline to end point [612]. Subjects taking nabilone also reported statistically significant improvements in anxiety, sleep, QoL, and overall patient status. Doses of nabilone ranged from 1 to 4 mg/day. Most subjects were concomitantly taking a variety of pain medications including NSAIDs, 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.

Dronabinol

A randomized, double-blind, placebo-controlled, crossover trial of patients suffering from MS-associated central neuropathic pain reported a decrease in central pain with 10 mg maximum daily doses of dronabinol [610]. 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% CI = 1.9 to 24.8). Fifty-four percent of patients had a ≥ 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. 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. 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.

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 [287]. 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. 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.

Nabiximols

Health Canada has approved Sativex® (with conditions) as an adjunct treatment for the symptomatic relief of neuropathic pain in MS [431].

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, MS-related) following treatment with nabiximols (Sativex®) [433, 834, 835]. In all three studies, patients were concomitantly using other drugs to manage their pain (anti-epileptics, tricyclic anti-depressants, opioids, NSAIDs, 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 non-medical purposes [834, 835]. 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 updated consensus statement and clinical guidelines on the pharmacological management of chronic neuropathic pain published by the Canadian Pain Society in 2014, cannabinoid-based therapies (e.g. dronabinol, nabiximols, smoked cannabis) are now considered to be third-line treatments (in 2007 they were considered fourth-line treatments) for neuropathic pain; mostly as adjuvant analgesics for pain conditions refractory to standard drugs [836, 837] (but also see **Section 4.8.3** and [838] for updated clinical guidelines on the use of cannabinoids for the treatment of symptoms associated with fibromyalgia).

A nine-month (38-week) open-label, add-on extension study investigated the long-term efficacy, safety and tolerability of nabiximols in 380 patients (234 completed) with peripheral neuropathic pain associated with diabetes mellitus or allodynia and concomitantly using other analgesic therapy [839]. One hundred and sixty-six patients had previously been taking nabiximols under a parent RCT (mean daily doses for allodynia, 8.9 sprays;

mean daily doses for diabetic neuropathy, 9.5 sprays). Mean daily dose of nabiximols in the add-on extension trial was between six and eight pump actuations (16.2 mg THC and 15 mg CBD and 21.6 mg THC and 20 mg CBD) and no increase in pump actuations was noted over time suggesting the absence of tolerance to the study medication. Eleven percent of patients who had received nabiximols during the parent RCT study withdrew from the extension study due to adverse events while 27% of patients taking placebo during the parent study withdrew from the extension study due to adverse events. Thirteen percent of patients who had received nabiximols in the parent RCT withdrew because of lack of efficacy. Concomitant analgesic medication was used by 84% of patients. The most commonly used analgesic medications included anticonvulsants, tricyclic anti-depressants, opioids, and NSAIDs. Non-analgesic concomitant medications included 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors, angiotensin-converting enzyme (ACE) inhibitors, biguanides, and platelet aggregation inhibitors. The vast majority of patients had a history of previously trying and failing at least one analgesic for their peripheral neuropathic pain (i.e. anticonvulsants and NSAIDs). All patients showed an improvement in pNRS score over time, from an initial score of 6.9 at baseline in the parent RCTs to a score of 4.2 at the end of the nine-month open-label extension trial period. At least half of the patients reported a 30% clinically significant improvement in pain compared to parent RCT baseline, and a minimum of 30% of patients demonstrated a 50% improvement in pain over time. The maximum reduction in pain scores occurred between 14 and 26 weeks during the extension trial. Improvements in sleep quality NRS scores and EQ-5D health questionnaire outcomes were maintained into and over the course of the add-on extension study period. The most common all-cause adverse events reported by system organ class were nervous system disorders (44%), GI disorders (36%), general disorders and administration site conditions (24%), infections and infestations (23%), and psychiatric disorders (21%). The most common treatment-related adverse events were dizziness (19%), nausea (9%), dry mouth (8%), dysgeusia (7%), fatigue (7%), somnolence (7%), and feeling drunk (6%). The majority (74%) of treatment-related adverse events resolved without consequence by the end of the study period. However, adverse events that were reported to be continuing at study end included fatigue, dizziness, and insomnia. Eleven percent of patients experienced a serious adverse event during the study, with 1% experiencing a treatment-related adverse event. The serious adverse events that were considered to be treatment-related included nervous system disorders and psychiatric disorders: two patients experienced amnesia, and there was one event of paranoia and one suicide attempt. Eighteen percent of patients ceased study medication due to treatment-related adverse events. The majority of these events occurred within the first week of treatment.

4.7.2.3 Cancer pain

- ***The limited available clinical evidence with certain cannabinoids (dronabinol, nabiximols) suggests a modest analgesic effect of dronabinol and a modest and mixed analgesic effect of nabiximols on cancer pain.***

Clinical studies with dronabinol

Two randomized, double-blind, placebo-controlled clinical 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 small dose-ranging study of 5, 10, 15, and 20 mg Δ^9-THC, given in successive days, to 10 cancer patients [840]. 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 [285]. 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 randomized, double-blind, placebo-controlled, parallel-group clinical trial of patients suffering from intractable cancer 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 [138]. Baseline daily median morphine equivalents ranged from 80 to 120 mg. Forty-three percent of patients (n = 60) taking the extract achieved a ≥ 30% improvement in their pain score, which was twice the number of patients who achieved this response in the THC only (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 that 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 pain refractory to strong opioid analgesics [283]. 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, 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 <u>and</u> neuropathic), followed by neuropathic pain (37%), and bone pain (28%). 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 vs. 14.5 for THC only. No dose escalation was noted in patients taking nabiximols beyond six months and up to one year following treatment initiation. 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 Brief Pain Inventory Short-Form was observed for both "pain severity" and "worst pain" over the five weeks of treatment. 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-C30, although some improvements in scores for sleep and pain, between baseline and week five of treatment, were reported. 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.

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 [284]. 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.

A randomized, placebo-controlled, cross-over pilot clinical trial of nabiximols for the alleviation of established chemotherapy-induced neuropathic pain reported no statistically-significant difference between the treatment and the placebo groups on a numerical rating scale for pain intensity (NRS-PI) [282]. The authors noted that five participants (responders) experienced a 2-point or greater drop in NRS-PI during treatment which was statistically significant compared to placebo. The mean dose of medication used in the treatment arm was eight sprays per day (range: 3 – 12) and 11 sprays in the placebo arm with most patients titrating to maximum dose in the placebo arm. Medication-related side effects were reported by the majority of participants and included fatigue, dry mouth, dizziness, nausea, headache, "fuzzy thinking" or "foggy brain", increased appetite and diarrhea. Ten participants continued into the extension phase of the trial and pain levels continued to decrease from a baseline of 6.9 to 5.0 at three months and 4.2 at six months. Average dose was 4.5 sprays per day (range: 2 – 10 sprays per day).

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 [431]. 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 [122, 138, 431], although higher numbers of sprays/day have been used or documented in clinical studies [284, 431]. It should be noted that increases in the number of sprays/day were accompanied by increases in the incidence of adverse effects.

4.7.2.4 "Opioid-sparing" effects and cannabinoid-opioid synergy

- ***While pre-clinical and case studies suggest an "opioid-sparing" effect of certain cannabinoids, epidemiological and clinical studies with oral THC and nabiximols are mixed.***
- ***Observational studies suggest an association between U.S. states with laws permitting access to cannabis (for medical and non-medical purposes) and lowered rates of prescribed opioids and opioid-associated mortality.***

The "opioid-sparing" effect refers to the ability of a non-opioid medication (e.g. cannabis, THC) to confer adjunctive opioid analgesia with the use of a lower dose of the opioid, thereby decreasing opioid-associated side effects. While there are some pre-clinical data and data from case studies supporting such an effect for cannabinoids, this is less well-established in published clinical studies. Furthermore, there is some evidence from epidemiological/observational studies to suggest that individuals using opioids for chronic non-cancer pain may also use cannabis to manage distress from unmanaged pain, and that a certain portion of individuals using higher doses of opioids for chronic non-cancer pain may also have greater problems across a number of domains, including greater risk of a CUD.

The following information summarizes the results from pre-clinical, epidemiological 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 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 GI motility, inhibition of locomotor activity, and anti-nociception [841-843]. 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 [841-843]. 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 [841]. This co-localization may play an important role in spinal-level modulation of peripheral nociceptive inputs [841]. Both receptors also share similar signal transduction molecules and pathways, the activation of which generally results in the inhibition of neurotransmitter release [841, 843]. The role of these receptors in inhibiting neurotransmitter release is further supported by their strategic localization on pre-synaptic membranes [841]. 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 [841]. 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 [844, 845]. 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 [846-848, 848-851]. A recent systematic review and meta-analysis of pre-clinical studies examining the strength of the existing evidence for the "opioid-sparing" effect of cannabinoids in the context of analgesia concluded that there was a significant opioid-sparing effect between morphine and THC when co-administered, although there was significant heterogeneity in the data [852]. Nevertheless, when compared to morphine administration alone, the median ED_{50} of morphine was 3.6 times lower when given in combination with THC. A significant "opioid-sparing" effect was also reported for THC when co-administered with codeine (ED_{50} 9.5 times lower when THC combined with codeine vs. codeine alone).

Clinical case series and epidemiological data

A recent cross-sectional on-line survey of 2 897 participants from a databse of 67 422 medical cannabis patients in the state of California gathered data about the use of cannabis as a substitute for opioid and non-opioid-based pain medication [853]. The majority of the participant sample reported being able to decrease the amount of opioids they consumed when they also used cannabis. Limitations of this study included self-report and very low response rate (4%) and a biased sample population.

Analysis of patients case-series reported a reduction in opioid dose with cannabis use in the treatment of chronic non-cancer pain [854]. In one case, a 47-year-old woman with a 10-year history of chronic progressive MS with headache, multi-site joint pain, bladder spasm, and leg spasticity on a daily regimen of 75 mg of long-acting morphine, 24 mg tizanidine, and 150 mg sertraline at bedtime began also using cannabis at bedtime. Over the next six months, the patient began smoking two to four puffs of cannabis at bedtime on a regular basis and reported a reduction of morphine to 45 mg per day, tizanidine to 6 mg per day, and sertraline to between 100 and 150 mg at bedtime. The patient reported improvement in pain, spasticity, bladder spasm, and sleep. The patient also reported not experiencing any adverse effects other than feeling somewhat “high” if she smoked more than four puffs at a time. Another patient, a 35-year-old male with HIV, who experienced HIV-related painful peripheral neuropathy involving the lower limbs and hands and who was taking 360 mg of long-acting morphine per day with an additional 75 mg of morphine sulfate four times daily for breakthrough pain and gabapentin at 2 400 mg per day began using smoked cannabis in a dose of three to four puffs, three to four times per day. Over the next four months, the patient’s dose of morphine decreased to 180 mg per day, and by nine months the patient discontinued the morphine followed by discontinuation of gabapentin. The patient also did not report any side effects associated with cannabis use. Lastly, a 44-year-old man with a six-year history of low back pain and left leg pain taking long-acting morphine at 150 mg per day and cyclobenzaprine 10 mg, t.i.d. with poor pain control began smoking cannabis, at a dose of several puffs to one joint, four to five times per day. After smoking cannabis on a regular basis for two weeks, the patient was able to decrease his morphine to 90 mg per day with a further reduction to 60 mg morphine per day and a reduction in cyclobenzaprine to 10 mg once daily with reported improvement in pain control. The authors of the case-series report that taken together, the three patients were able to reduce their opioid dose by 60 to 100% after starting the cannabis regimen. In addition, patients self-reported experiencing better pain control with the introduction of cannabis into their pain management strategy. All patients reported previous cannabis use before onset of morbidity.

A prospective, non-randomized, and unblinded observational case-series study assessing the effectiveness of adjuvant nabilone therapy in managing pain and symptoms experienced by 112 advanced cancer patients in a palliative care setting reported that those patients using nabilone had a lower rate of starting NSAIDs, tricyclic anti-depressants, gabapentin, dexamethasone, metoclopramide, and ondansetron and a greater tendency to discontinue these drugs [288]. Patients were prescribed nabilone for pain relief (51%), for nausea (26%), and for anorexia (23%). Treated patients were started on 0.5 or 1 mg nabilone at bedtime during the first week and titrated upwards in increments of 0.5 or 1 mg thereafter. At follow-up, the majority of patients were on a 2 mg daily nabilone dose with a mean daily dose of 1.79 mg. The two primary outcomes of the study, pain and opioid use in the form of total morphine sulfate equivalents were reduced significantly in treated patients compared to untreated patients. Side effects from nabilone consisted mainly of dizziness, confusion, drowsiness, and dry mouth. Patients also demonstrated less tendency to initiate additional new medications and could reduce or discontinue baseline medications.

A time-series analysis that examined death certificate data over time (1999-2010) between U.S. states with medical cannabis programs and those without, to determine if there was an association between the presence of state medical cannabis laws and opioid analgesic overdose mortality rates, reported that age-adjusted opioid analgesic overdose death rate per 100 000 population in states that enacted medical cannabis laws was almost 25% lower than in states without such laws (95% CI = -37.5%, -9.5%) [855]. This association appeared to strengthen over time, with a decrease in the mean annual opioid overdose mortality rate of 19.9% in the first-year and a decrease in the mean annual opioid overdose mortality rate of 33.3% in year six after enactment of state medical cannabis laws. This study appears to suggest that medical cannabis laws are associated with reductions in opioid analgesic overdose mortality on a population level, however the mechanisms by which this appears to occur is unclear at this time and requires further investigation.

A time-series analysis that examined the association between Colorado’s legalization of cannabis for non-medical purposes and opioid-related deaths (2000-2015) reported a 0.7 deaths/per month reduction in opioid-related deaths ($b = –0.68$; 95% CI = –1.34, –0.03). Specifically, there was a 6% decrease in opioid-related deaths two years following legalization of non-medical cannabis when compared to two control states (one allowing cannabis for medical purposes, one not allowing cannabis for medical or non-medical purposes). However, the authors note that the two-year follow-up window post-legalization is relatively short and further research involving longer follow-up periods (and examining additional states that have legalized cannabis for non-medical purposes) are needed to determine if these reductions are sustained or dissipate over time [856].

Two recent observational studies using U.S health care data (Medicare and Medicaid) examined the difference in opioid prescription rates in U.S. states with and without legal access to cannabis. Bradford and colleagues [857] longitudinally (2010-2015) found that states that implemented medical cannabis laws reported fewer daily doses of prescribed opioids (2.21 million/year) compared to states without medical cannabis laws. Parallel to this finding, Wen and Hockenberry [858] cross-sectionally found that states with medical cannabis laws reported a 5.88% lower rate of prescribed opioids. This study further examined opioid prescribing patterns in states with laws regarding cannabis for non-medical purposes, and found that access to cannabis was also associated with reductions in opioid prescribing rates (i.e., 6.38% lower compared to states without non-medical cannabis legalization). Key limitations across these studies are the associative nature of the findings meaning that causality cannot be established, and the inability to determine if cannabis actually replaced or substituted for opioid use, as users potentially could have accessed and used opioids from other non-medical sources.

A cross-sectional retrospective survey of 244 patients accessing cannabis for medical purposes at a Michigan dispensary reported that the use of cannabis for medical purposes was associated with a significant decrease in opioid use, as well as a decrease in the number of other medications used and in the number of side effects associated with the use of other medications, as well as improvements in QoL [859]. The majority (80%) of the study participants reported smoking cannabis daily. The mean decrease in self-reported opioid use among all study respondents was 64%. Furthermore, there was a statistically significant decrease in the number of other non-opioid medications (e.g. NSAIDs, disease-modifying anti-rheumatic drugs, anti-depressants, serotonin-norepinephrine reuptake inhibitors, and selective serotonin reuptake inhibitors) after cannabis use. Limitations of the study include potential recall bias, a self-selected population, self-report, and changes in the rates of physician prescription of opioids.

A prospective, open-label, single-arm, longitudinal study of 274 patients with treatment-resistant chronic pain (i.e. musculoskeletal widespread pain, peripheral neuropathic pain, radicular low back pain, cancer pain), examined the long-term effect of medicinal cannabis treatment on pain and functional outcomes [582]. Intention-to-treat analysis was conducted on 206 patients who provided baseline data and 176 subjects completed the study and were included in the final analysis. Patients could use smoked cannabis, baked cookies or an olive oil extract as drops (up to a maximum equivalent of 20 g per month, but with the possibility of increasing this amount if warranted). Patients were instructed to titrate their cannabis dose starting with one cigarette puff (or one drop of cannabis oil) per day and increase by increments of one puff or drop per dose up to three times per day until satisfactory pain relief was achieved or side effects appeared. Subjects were instructed to refrain from driving for at least 6 h after consuming cannabis or longer if they felt disoriented or drowsy. THC concentrations in the smoked product were estimated at 6 – 14% THC and between 11 – 19% in the oral formulations, with the CBD concentrations between 0.2 – 3.8% in the smoked product and 0.5 – 5.5% in the oral formulations. Mean monthly-prescribed amount of cannabis at follow-up was 43 g (average of 1.4 g per day). Cannabis treatment was added to the existing analgesic regimen. Median daily dose among opioid users (in daily oral morphine sulfate equivalents) was 60 mg. At follow-up (mean of seven months from treatment start), pain symptom score improved from a median score of 83.3 to a median score of 75.0 ($p < 0.001$) on the Short-Form Treatment Outcomes in Pain Survey (S-TOPS) questionnaire with 66% of subjects reporting improvement, 8% reporting no change, and 26% reporting deterioration. In subgroup analyses, no differences were noted in the primary outcome between neuropathic and non-neuropathic pain, or between male and female patients. Improvements were also noted in Brief Pain Inventory (BPI) scores of pain severity and pain interference as well as with most social and emotional disability scores (i.e. S-TOPS scores for family-social disability, role-emotional disability, satisfaction with outcomes, sleep problem index). Opioid consumption at follow-up also decreased by 44%. The median (daily) oral morphine equivalent dose among subjects still receiving opioids at follow-up decreased from 60 mg to 45 mg but did not reach statistical significance. Nine subjects discontinued treatment due to mild to moderate adverse effects, mainly sedation, heaviness, nervousness, and difficulty concentrating. Two additional subjects discontinued treatment due to serious side effects: one because of elevated liver transaminases, and one elderly subject admitted to emergency care and hospitalized for confusion. Total rate of cannabis discontinuation was 5.3%. Study limitations included lack of a control group and open-label design, lack of frequent periodic assessment of all adverse events, and under-representation by women.

Findings from a two-year, prospective, cross-sectional, cohort study of 1 514 individuals prescribed pharmaceutical opioids for chronic non-cancer pain (the Pain and Opioids IN Treatment study) examined the extent to which cannabis is used by this group [214]. The study reported that one in six (16%) enrolled individuals had used cannabis for pain relief and 25%, reported they would have used it for pain relief if they had access. Among those using cannabis for pain, the average pain relief they reported from using cannabis was 70%, which was in contrast to the 50% average pain relief reported for opioid medications. Almost half (43%) had used cannabis for non-medical purposes at some time and 12% of the entire cohort met the criteria for an International Classification of Diseases (ICD) CUD in their lifetime. Those individuals reporting using cannabis for pain relief were on average younger and male, and were significantly more likely to have met criteria for a range of other licit and illicit substance use disorders and to meet criteria for moderate or severe depression and generalized anxiety. Individuals who had used cannabis for pain were more likely to have reported back and neck problems and had been living with pain for a significantly longer period compared to those not using cannabis for pain. Those who had used cannabis for pain reported greater pain severity, greater interference from and poorer coping with pain, and more days out of role in the past year compared to those who had not used. In addition, these individuals had been prescribed opioids for longer, were on higher opioid doses, were more likely to also have been prescribed benzodiazepines, and were more likely to be non-adherent with their opioid use. According to the authors, those individuals using cannabis for pain appeared to be a group with greater problems across a number of domains including psychological distress and substance use problems such that the use of cannabis for pain may reflect those characteristics. Alternatively, the authors suggest that the adjunctive use of cannabis for pain could reflect attempts by those individuals to manage distress, given the experience of greater interference from reported pain. Limitations of the study include potential for under-reporting, potential bias associated with self-reporting, and lack of information on amount of cannabis consumed and potency.

In support of the above findings, a study looking at the rates of CUD in a national sample of Veterans Health Administration patients (N = 1 316 464) with chronic non-cancer pain diagnoses and receiving opioid medications, suggested that greater numbers of prescription opioid fills were associated with greater likelihood of a diagnosis of a CUD [860]. Patients prescribed opioids and diagnosed with a CUD were found to be significantly younger and more likely to be homeless. Those diagnosed with a CUD were also more likely to be diagnosed with hepatic disease and HIV, though less likely to be diagnosed with dementia and renal disease compared to those without a CUD. Patients diagnosed with a CUD were also more likely to be diagnosed with schizophrenia, other psychotic disorders, bipolar disorder, major depressive disorder, anxiety disorders, adjustment disorder, personality disorder, and dual diagnosis. Those with a CUD were also more likely to have been diagnosed with abuse or dependence of hallucinogens, cocaine, tobacco, amphetamine, opioids or alcohol. The authors conclude that the results of this study suggest that rather than cannabis functioning as an opioid substitute (i.e. CUD would be associated with less opioid use), these substances appear to complement each other as greater opioid medication use is associated with increased risk of CUD. Limitations of this study included a mostly homogenous population sample (male military veterans), and reliance on non-standardized semi-structured diagnostic interviews, raising the possibility that the actual prevalence of CUD in this patient population was under-estimated.

An epidemiological study using data gathered from wave 1 and 2 of NESARC (2001 – 2002 and 2004 – 2005) prospectively examined the association between cannabis use and incident non-medical prescription opioid use and disorder 3 years later, as well as whether cananbis use among adults with non-medical prescription opioid use was associated with subsequent decrease in non-medical opioid use [861]. Cannabis use at wave 1 was associated with a significant increase in the odds of prevalent non-medical prescription opioid use during the follow-up period at wave 2 which persisted even after adjusting for confounders. This association was observed among adults without past-year cannabis use disorder and among adults with moderate or more severe pain at wave 1. Furthermore, among individuals without non-medical opioid use during the 12 months prior to the wave 1 interview, there was a significant association between cannabis use at wave 1 and incident non-medical opioid use during the follow-up period. Cannabis use also appeared to be associated with lower odds of decreasing levels of opioid use but decreases were markedly more common than increases in opioid use. After adjustment for other covariates, significant associations persisted between wave 1 cannabis use and prevalent and incident non-medical opioid use disorder at wave 2. Among adults with moderate or more severe pain at wave 1, cannabis use was associated with prevalent opioid use disorder in adjusted analyses. Despite the above findings, the great majority of adults who used cannabis did not go on to initiate or increase non-medical opioid use.

A preliminary, historical, small cohort study examined the association between enrollment in a medical cannabis program and prescription opioid use [862]. Enrollment in a medical cannabis program was associated with a statistically significant higher odds of ceasing opioid prescriptions (OR = 17.27, CI = 1.89, 157.36), an OR = 5.12 of reducing daily opioid doses (CI = 1.56, 16.88). Improvements were noted in pain reduction, quality of life, social life, activity levels, and concentration with few side effects.

Data from clinical trials

A recent systematic review and meta-analysis of clinical studies examining the strength of the existing evidence for the "opioid-sparing" effect of cannabinoids in the context of analgesia concluded that there was an absence of randomized, well-controlled clinical studies that provide evidence of an "opioid-sparing" effect of cannabinoids [852]. Furthermore, the existing data from clinical trials looking at the "opioid-sparing" ability of cannabis are mixed. One double-blind, placebo-controlled, crossover clinical 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 [863]. 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. 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.

A recent double-blind, placebo-controlled, within-subject clinical study examined if cannabis enhances the analgesic effects of (low dose) oxycodone and the impact of combining cannabis and oxycodone on abuse liability. Eighteen healthy 'current' cannabis smokers (at least 3 times/week; assessed by urine toxicology and self-report) were given oxycodone (0, 2.5, and 5.0 mg, P.O.) with smoked cannabis (0.0, 5.6% THC), and the analgesic effects were measured by the Cold-Pressor Test. Results revealed that oxycodone alone (5.0 mg) significantly increased pain threshold ($F [1, 17] = 7.5$, $p \leq 0.01$) and tolerance ($F [1, 17] = 5.4$, $p \leq 0.05$) compared to placebo (inactive cannabis and 0.0mg oxycodone). When administered with active cannabis, 5.0 mg oxycodone also increased pain tolerance compared to the placebo condition and active cannabis alone ($F [1, 17] = 5.5$, $p \leq 0.05$). The combination of active cannabis and 2.5 mg oxycodone increased pain threshold and tolerance relative to the placebo condition ($F [1, 17] = 5.9$, $p \leq 0.05$ and $F [1, 17] = 6.5$, $p \leq 0.05$, respectively) and active cannabis alone ($F [1, 17] = 5.2$, $p \leq 0.05$ and $F [1, 17] = 5.5$, $p \leq 0.05$, respectively). In terms of abuse liability oxycodone did not increase subjective ratings of cannabis abuse or cannabis self-administration. However, a combination of oxycodone (2.5 mg) and cannabis yielded small but significant increases in oxycodone abuse liability ($p \leq 0.05$). The researchers concluded that the findings demonstrate opioid-sparing effects of cannabis for analgesia that may be accompanied by increases in potential abuse liability pertaining to oxycodone [864].

Another clinical study [287] 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 4.7.2.2**, under Clinical Studies With Orally Administered Prescription Cannabinoids).

In another study, 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%, CI = 9 – 46) following inhalation of vapourized cannabis (900 mg, 3.56% THC, t.i.d. for five days) [280] (for additional details see **Section 4.7.2.2**, 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.

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 [138]. 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 [284]. However, the design of the latter study did not allow proper assessment of an "opioid-sparing effect" of nabiximols.

In summary, pre-clinical and case studies appear to support an "opioid-sparing" effect of THC but results from clinical and epidemiological studies are mixed. 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, some of the evidence is mixed and requires further study [841, 843].

4.7.2.5 Headache and migraine

- ***The evidence supporting using cannabis/certain cannabinoids to treat headache and migraine is very limited and mixed.***

With regard to migraine, an endocannabinoid deficiency has been postulated to underlie the pathophysiology of this disorder [865]; however, the evidence supporting this hypothesis is limited and mixed. Clinical studies suggest that the concentrations of anandamide are decreased in the CSF of migraineurs, while the levels of calcitonin-gene-related-peptide and nitric oxide (normally inhibited by anandamide and implicated in triggering migraine) are increased [866, 867]. In contrast, the activity of the anandamide-degrading enzyme FAAH is significantly decreased in chronic migraineurs compared to controls [868].

While historical and anecdotal evidence suggest a role for cannabis in the treatment of headache and migraine [869], no controlled clinical studies of cannabis or prescription cannabinoids to treat headache or migraine have been carried out to date [870, 871].

In one case-report, a patient suffering from pseudotumour cerebri and chronic headache reported significant pain relief after smoking cannabis [293]. 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) [291]. However, these single-patient case-studies should be interpreted with caution.

A 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 [290].

A retrospective chart review of 121 adults with a primary diagnosis of migraine headaches who were recommended migraine treatment or prophylaxis with cannabis for medical purposes by a physician from among two medical cannabis specialty clinics in Colorado reported that migraine headache frequency decreased from 10.4 to 4.6 headaches per month ($p < 0.0001$) with the use of cannabis for medical purposes [289]. Forty percent of the patients reported positive effects with the most common effect being prevention of migraine headache, decreased frequency, and aborted migraine headache. Inhaled cannabis was reported as being more effective than oral ingestion. Negative effects were reported in 12% of patients, with edibles being associated with more negative effects (i.e. problems with timing and effect intensity).

It should also be noted that cannabis use has been associated with reversible cerebral vasoconstriction syndrome and severe headache [292]. In addition, headache is an often-observed adverse effect associated with the use of cannabis or prescription cannabinoid medications [59, 227, 431, 492, 688, 716], and headache is also one of the most frequently reported physical symptoms associated with cannabis withdrawal [872].

A recent review of the use of cannabis for headache disorders reported that there is insufficient evidence from well-controlled clinical trials to support the use of cannabis for headache, despite sufficient anecdotal and preliminary results as well as plausible neurobiological mechanisms to warrant clinical studies [873].

4.8 Arthritides and musculoskeletal disorders

- ***The evidence from pre-clinical studies suggests stimulation of CB_1 and CB_2 receptors alleviates symptoms of osteoarthritis (OA), and THC and CBD alleviate symptoms of rheumatoid arthritis (RA).***
- ***The evidence from clinical studies is very limited, with a modest effect of nabiximols for RA.***
- ***There are no clinical studies of cannabis for fibromyalgia, and the limited clinical evidence with dronabinol and nabilone suggest a modest effect on decreasing pain and anxiety, and improving sleep.***
- ***The role of cannabinoids in osteoporosis has only been investigated pre-clinically and is complex and conflicting.***

The arthritides include a broad spectrum of different disorders (e.g. osteoarthritis (OA), rheumatoid arthritis (RA), ankylosing spondylitis, gout, and many others) all of which have in common the fact that they target or involve the joints. Scientific studies have demonstrated that joints, bone, and muscle all contain a working ECS, that some arthritides such as OA and RA are associated with changes in the functioning of the ECS, and that modulation of the ECS may help alleviate some of the symptoms associated with certain arthritides [40-42, 778, 874-882]. The section below summarizes the evidence for cannabis/cannabinoids in OA and RA. Also covered are musculoskeletal disorders such as fibromyalgia and osteoporosis.

Information from surveys

The 2011 **C**anadian **A**lcohol and **D**rug **U**se **M**onitoring **S**urvey (**CADUMS**) indicated that a significant proportion of Canadians aged 15 and over who reported using cannabis for medical purposes reported using it for chronic pain associated with, for example, arthritis [883].

In addition, one study that explored the experiences of Australian individuals using cannabis for medical purposes reported that out of 128 participants in the survey, 35% said they used cannabis to treat symptoms associated with arthritis [884].

A self-administered survey of 947 individuals in the U.K. who reported ever having used cannabis for medical purposes revealed that 21% of the individuals surveyed said they had used cannabis for symptoms associated with arthritis. Seven percent of these individuals had been using cannabis continuously for a median of four years [579].

A survey of 628 Canadian individuals who self-reported using cannabis for medical purposes asked about individuals' use of cannabis for medical purposes [885]. Approximately 15% of individuals reporting using cannabis for medical purposes used it to treat symptoms associated with arthritis pain, inflammation, insomnia, anxiety, depression, and spasms. Most reported preferring smoking (53%) compared to vapourizing or oral ingestion (both at 39%). The majority (47%) of individuals using cannabis for arthritis reported using cannabis four or more times per day and an equal proportion reported using at least 2 g per day or more; the median gram amount among those that used 2 g per day or more was approximately 4 g per day.

4.8.1 Osteoarthritis

Among the arthritides, OA is by far the most common type of arthritis and is the leading cause of disability in those over the age of 65 years in developed countries [886]. OA results from damage to the articular cartilage induced by a complex interplay of genetic, metabolic, biochemical and biomechanical factors followed by activation of inflammatory responses involving the interaction of the cartilage, subchondral bone and synovium resulting in further damage and degradation of the articular cartilage and subchondral bone, variable synovitis, and capsular thickening [877, 878]. The eventual outcomes are joint disability and severe pain [877, 878]. The pain associated with OA is generally inadequately or safely controlled with current analgesics, which has spurred the search for alternative therapeutic approaches [878]. The disease affects both men and women, although it appears to occur more frequently in women [877]. In addition, OA most commonly affects people in middle age and the elderly, even though younger people may also be affected due to injury or overuse [877]. The pain associated with OA includes both nociceptive and non-nociceptive components, as well as neuropathic and inflammatory components, and is associated with abnormally excitable pain pathways in the peripheral nervous system and the CNS [877]. The pain and physical disability associated with OA are also accompanied by anxiety, depression and changes in cognition all of which have a negative impact on QoL [876]. Neuroimaging studies have shown that several brain regions are involved in the processing of OA pain including bilateral activation of primary and secondary somatosensory cortices as well as the insular, cingulate, pre-frontal and orbito-frontal cortices, and the thalamus, as well as unilateral activation of the putamen and amygdala [887, 888].

Pre-clinical studies

Animal models of OA suffer from a number of limitations such as differences in anatomy, functionality, dimensions, cartilage repair processes, and thickness in comparison with human joints [877]. In addition, the lesions that develop in animal models of OA correspond to those found in humans only in a particular stage of the disease [877]. Furthermore, no animal model of OA completely reproduces the whole variety of signs and symptoms of human OA. Taken together, these factors all pose a number of significant challenges in translating findings obtained in animal models of OA to OA patients. Nevertheless, animal models of OA are useful in understanding the potential therapeutic effects of cannabis and cannabinoids.

There is increasing evidence that suggests an important role for the ECS in the pathophysiology of joint pain associated with OA [877]. With regard to endocannabinoid tone, one animal study reported elevated levels of the endocannabinoids anandamide and 2-AG, and the "entourage" compounds PEA and OEA in the spinal cord of rats with experimentally-induced knee joint OA [889]. While no changes were observed in the levels or the activities of the endocannabinoid catabolic enzymes FAAH or MAGL in the spinal cord of the affected rats, protein levels of the major enzymes responsible for endocannabinoid synthesis were reported to be significantly elevated in these animals [889].

Both CB_1 and CB_2 receptors have been localized in knee joints confirming that local control of joint pain is achievable without the need to involve central cannabinoid receptors [890, 891]. Downregulation of CB_1 and CB_2 receptor gene expression was reported in the lumbar spinal cord of osteoarthritic mice, likely in response to an elevated endocannabinoid tone coming from the affected osteoarthritic joints [892].

A study in rats reported that intra-articular injection of the CB_1 receptor agonist arachidonyl-2-chloroethylamide in control animals was associated with a reduction in firing rate and suppression of nociceptive activity from pain fibers innervating the joints when the joints were subjected to either normal or noxious joint rotation [893]. Furthermore, animals with osteoarthritic joints produced an augmented response to articular CB_1 receptor activation. The anti-nociceptive effect was blocked by co-administration of a CB_1 receptor antagonist in osteoarthritic joints, but not in control joints.

Local administration of URB597 (a FAAH inhibitor) by intra-arterial injection proximal to an osteoarthritic joint was associated with decreased mechanosensitivity of joint afferent fibres in two different rodent models of OA [894]. Behavioural experiments carried out in OA rats suggested that treatment with the inhibitor also decreased joint pain measured by a decrease in hindlimb incapacitance [894]. In addition to an antinociceptive response to FAAH inhibition, URB597 has been shown to reduce leukocyte trafficking in the synovium indicating that endocannabinoids could have anti-inflammatory properties in joints [880].

Systemic administration of a CB_2 receptor agonist in a rat model of OA was associated with a dose-dependent reversal of decreased grip force in the affected limb, a proxy measure for pain [895]. The maximal analgesic efficacy was comparable to that seen with celecoxib in this animal model of OA [895].

In another animal study, the spinal lumbar CB_2 receptor was shown to play a significant role in the modulation of osteoarthritic pain [892]. Furthermore, upregulation of CB_2 receptor expression in the spinal lumbar cord was associated with attenuation of joint pain. In addition, lumbar spinal cord mu-opioid receptor expression was downregulated, while delta and kappa-opioid receptor expression was upregulated, suggesting functional interactions between the endocannabinoid and opioid systems. The decreased mu-opioid receptor expression and concomitant increase in kappa and delta opioid receptor expression could additionally contribute to the nociceptive component of the disease.

One animal study conducted in a rat model of OA reported that CB_2 receptor mRNA levels were significantly increased in spinal cord of osteoarthritic rats [896]. Furthermore, selective stimulation of the CB_2 receptor by systemic dosing with a synthetic cannabinoid receptor agonist was associated with significant attenuation of the development and maintenance of pain behaviour and spinal neuronal responses. Levels of pro-inflammatory cytokines such as interleukin (IL)-1β, tumor necrosis factor (TNF) α, and IL-10 were also significantly attenuated following treatment with the CB_2 receptor agonist. Rats also did not appear to develop tolerance to the anti-nociceptive effects of the CB_2 receptor agonist after multiple administrations of the drug. The study also showed a negative association between CB_2 mRNA levels and chondropathy in *post-mortem* samples of human spinal cord.

An animal study of OA in mice reported that the condition was associated with significant increases in 2-AG levels in the prefrontal cortex, the area of the brain implicated in pain, cognitive and emotional processing, as well as in the plasma [876]. OA in this mouse model was also associated with increases in stress and anxiety-like behaviour in affected wild-type mice and in mice lacking CB_1 receptor expression, but not in mice lacking CB_2 receptor expression suggesting distinct roles for these two receptors in the pathophysiology of OA. Selective stimulation of CB_1 and CB_2 receptors was associated with improvements in mechanical allodynia. Lastly, patients with OA were shown to have significant increases in their plasma levels of 2-AG, but not anandamide, compared to healthy controls consistent with the findings obtained in the mouse model. Furthermore, expression of CB_1 and CB_2 receptors was upregulated in blood lymphocytes of these patients and significant positive correlations were noted between plasma levels of 2-AG, knee pain, and depression scores as well as significant negative correlations with SF-36 (QoL) and memory performance scores.

Further support for a role for the CB_2 receptor in the pathophysiology of OA comes from a pre-clinical study in mice lacking CB_2 receptor expression [897]. These mice developed significantly more severe OA compared with wild-type controls. Furthermore, treatment of wild-type mice with a CB_2 receptor agonist was associated with partial protection from OA. In contrast, another study found that local delivery of a CB_2 receptor agonist actually increased joint nociceptor activity and the resulting heightened pain response was thought to involve TRPV1 ion channels [891].

A pre-clinical study in rats that investigated the effects of CBD on intravertebral disc degeneration showed that direct intradiscal injection of 120 nmol of CBD, but not lower doses of 30 or 60 nmol CBD, immediately after disc lesion significantly attenuated the extent of disc injury and the beneficial effect was maintained up to 15 days' post-injury [898].

Clinical studies

There are no published clinical studies of cannabis for OA. In humans, one study found that the levels of the endocannabinoids anandamide and 2-AG in the synovial fluid of patients with OA were increased compared to non-inflamed normal controls, although the significance of these findings remains unclear [42].

One multi-centre, randomized, double-blind, double-dummy, placebo- and active-controlled crossover clinical trial of a FAAH inhibitor reported a lack of analgesic activity (Western Ontario and McMaster Universities pain score) in patients with OA of the knee [899]. In contrast, administration of naproxen in the study was associated with significant analgesia. Importantly, this clinical trial raised serious questions about the translatability of findings from animal studies to those conducted with humans since the FAAH inhibitor had shown efficacy in the animal model but not in humans. In addition, other issues of concern include the testing of the FAAH inhibitor on a heterogeneous population of OA patients and off-target effects (e.g. at TRPV1).

4.8.2 Rheumatoid arthritis

RA is a destructive, systemic, auto-immune inflammatory disease that affects a smaller, but not insignificant, proportion of the adult population [886]. It is characterized by chronic inflammatory infiltration of the synovium leading to progressive synovitis, and eventual cartilage and joint destruction, functional disability, significant pain, and systemic complications (e.g. cardiovascular, pulmonary, psychological, and skeletal disorders such as osteoporosis) [879, 900, 901]. As with OA, the ECS plays an important role in the pathophysiology of the disorder and manipulation of the ECS holds therapeutic promise.

Pre-clinical studies

A pre-clinical study in a rat model of RA reported that treatment with either THC or anandamide was associated with significant anti-nociception in the paw-pressure test [382]. Another study in two different mouse models of RA (acute and chronic) reported that systemic administration (i.p.) of a range of doses of CBD (2.5 mg/kg, 5 mg/kg, 10 mg/kg, 20 mg/kg per day), after onset of acute arthritic symptoms, for a period of 10 days, was associated with the cessation of the progression of such symptoms [902]. The daily 5 mg/kg i.p. dose was deemed to be the optimal dose for both acute (10 days) and chronic models (5-weeks) of arthritis. No obvious side effects were noted at any of the tested doses. Oral administration of 25 mg/kg of CBD for 10 days after onset of acute arthritic symptoms was associated with suppression of the progression of these symptoms, although the 50 mg/kg daily oral dose was almost equally effective. The 25 mg/kg daily oral dose was also effective in suppressing the progression of chronic arthritic symptoms when administered over a five-week period. Protective effects associated with exposure to CBD included the prevention of additional histological damage to arthritic hind-paw joints, suppression of TNF release from arthritic synovial cells, attenuation of lymph node cell proliferation, suppression of production of reactive oxygen intermediates and attenuation of lymphocyte proliferation.

The results from a study examining the anti-nociceptive effects of THC in a rat model of RA suggested that intraperitoneal administration of 4 mg/kg THC was associated with a significant decrease in the levels of spinal dynorphin, an increase in kappa-opioid receptor-mediated analgesia, and a decrease in NMDA-receptor-mediated hyperalgesia [903]. Another study by the same group and using the same animal model demonstrated that THC was equipotent and equiefficacious to morphine with regard to anti-nociception in the paw-pressure test, and that there was a synergistic anti-nociceptive interaction between THC and morphine in both arthritic and non-arthritic rats in the same paw-pressure test [384]. A follow-up study again using the same animal model suggested an important role for the CB_2 receptor in modulating the anti-nociceptive effects of THC [904].

Indeed, a number of additional studies have continued to support an important role for the CB_2 receptor in RA [874, 879, 905]. Tissue samples taken from human rheumatoid joints showed increased CB_2 receptor expression compared to osteoarthritic joints, with expression of the CB_2 receptor localized to the lining layer and interstitial sub-lining layer as well as follicle-like aggregates [879, 905]. Furthermore, CB_2 receptor activation on fibroblast-like synoviocytes derived from rheumatoid joints was associated with inhibition of the production of a variety of inflammatory mediators seen in RA including IL-6, matrix metalloproteinase (MMP)-3, MMP-13, and chemokine (C-C motif) ligand (CCL) 2 [879, 905]. CB_2 receptor activation was also associated with dose-dependent amelioration of arthritis severity in a mouse model of RA [905]. Selective stimulation of the CB_2 receptor significantly decreased joint swelling, synovial inflammation, and joint destruction, as well as serum levels of anti-collagen II antibodies in a mouse model of RA [874]. However, others have reported that stimulation of joint CB_2 receptors causes synovial hyperaemia through a mechanism involving TRPV1 ion channels [906]. The vasodilator effect of these CB_2 receptor agonists is attenuated in models of acute and chronic arthritis suggesting that CB_2 receptors are downregulated in inflamed joints.

A recent pre-clinical study examined the efficacy of transdermal CBD for the reduction of inflammation and pain in a rat model of RA [907]. In this study, gel preparations containing increasing doses of CBD (0.6, 3.1, 6.2, 62.3 mg/day) were applied to the dorsal skin surface for four consecutive days after induction of rheumatoid-like arthritis. Transdermal absorption resulted in dose-dependent increases in plasma concentrations of CBD. Four consecutive days of application resulted in mean plasma concentrations of 3.8 ng/mL, 17.5 ng/mL, 33.3 ng/mL, and 1 629.9 ng/mL, respectively. The three lower doses exhibited linear pharmacokinetic correlations, but not the highest dose. Furthermore, the 6.2 mg and the 62.3 mg gel doses of CBD significantly reduced joint swelling, limb posture scores as a rating of spontaneous pain, immune cell infiltration and thickening of the synovial membrane. The 6.2 mg dose of CBD optimally reduced swelling and synovial membrane thickness. CBD treatment was not associated with changes in exploratory behaviour suggesting the lack of psychoactive effects.

Clinical studies

In humans, one study found that the levels of the endocannabinoids anandamide and 2-AG in the synovial fluid of patients with RA were increased compared to non-inflamed normal controls, although the significance of these findings remains unclear [42].

There are no published clinical studies of cannabis for RA.

A preliminary clinical study assessing the effectiveness of nabiximols (Sativex®) for pain caused by RA reported a modest but statistically significant analgesic effect on movement and at rest, as well as improvement in quality of sleep [383]. Administration of nabiximols was well tolerated and no significant toxicity was observed. The mean daily dose in the final treatment week was 5.4 pump actuations (equivalent to 14.6 mg THC and 13.5 mg CBD/day, treatment duration was three weeks). The differences observed were small and variable across the participants.

A Cochrane Collaboration review conducted in 2012 concluded that the evidence in support of the use of oro-mucosal cannabis (e.g. nabiximols) for the treatment of pain associated with RA is weak and given the significant side effect profile typically associated with the use of cannabinoids, the potential harms seem to outweigh any modest benefits achieved [900].

4.8.3 Fibromyalgia

Fibromyalgia is a disorder characterized by widespread pain (allodynia and hyperalgesia) and a constellation of other symptoms including sleep disorders, fatigue, and emotional or cognitive disturbances [908]. While the underlying pathophysiology of fibromyalgia remains unclear, disturbances in the recruitment or functioning of peripheral and central pain processing pathways and in the levels of several important neurotransmitters (serotonin, noradrenaline, dopamine, opioids, glutamate and substance P) have been noted in fibromyalgia patients [909-912]. Co-morbid depressive symptoms have also been associated with a more pronounced deficit in pain inhibition, as well as increased pain in fibromyalgia patients [913].

Clinical studies with smoked or orally ingested cannabis

There are no clinical trials of smoked or ingested cannabis for the treatment of fibromyalgia. However, a cross-sectional survey of patients suffering from fibromyalgia found that the patients reported using cannabis (by smoking and/or eating) to alleviate pain, sleep disturbance, stiffness, mood disorders, anxiety, headaches, tiredness, morning tiredness, and digestive disturbances associated with fibromyalgia [184]. Subjects (mostly middle-aged women who did not respond to current treatment) reported statistically significant decreases in pain and stiffness, and statistically significant increases in relaxation and well-being 2 h after cannabis self-administration. Side effects included somnolence, dry mouth, sedation, dizziness, high, tachycardia, conjunctival irritation, and hypotension. The study suffered from a number of limitations including the study design, small sample size, variability in frequency and duration of cannabis use, and a biased subject population.

Clinical studies with prescription cannabinoid medications

There are relatively few properly controlled clinical studies examining the role of cannabinoids in the treatment of fibromyalgia. The available evidence is summarized below.

Dronabinol

A non-placebo controlled pilot study examining the effect of dronabinol monotherapy (2.5 – 15 mg Δ^9-THC/day; with weekly increases of 2.5 mg Δ^9-THC, up to a maximum of 15 mg THC/day) on experimentally-induced pain, axon reflex flare, and pain relief in patients suffering from fibromyalgia reported that a sub-population of such patients experienced significant pain relief (reduced pain perception) with 10 and 15 mg/day Δ^9-THC, but no changes were observed in axon reflex flare [385]. Touch-evoked allodynia and pinprick-induced hyperalgesia were also not significantly affected by Δ^9-THC. Subjects who completed a three-month course of therapy (15 mg/day Δ^9-THC) reported a > 50% decrease in pain. The study however suffered from low power due to the high rate of patient drop-out caused by intolerable side effects of the treatment.

A multi-center, retrospective study of patients suffering from fibromyalgia who were prescribed an average daily dose of 7.5 mg Δ^9-THC, over an average treatment period of seven months, reported a significant decrease in pain score, a significant decrease in depression, and a reduction in the intake of concomitant pain-relief medications such as opioids, anti-depressants, anti-convulsants, and NSAIDs following treatment with Δ^9-THC [386]. It is important to note that the study had a number of considerable limitations (method of data collection, heterogeneous patient selection criteria, and high subject dropout rate) and as such, the results should be interpreted with caution.

Nabilone

A randomized, double-blind, placebo-controlled clinical 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 [596]. 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) [914]. Patients were taking concomitant pain medications such as NSAIDs, 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 clinical study of 29 patients suffering from fibromyalgia reported that nabilone (0.5 – 1.0 mg before bedtime) improved sleep in this patient population [597].

The 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) [838]. For additional information regarding the use of cannabis/cannabinoids to alleviate sleep disorders or disturbances, please consult **Section 4.9.5.2**.

A Cochrane systematic review of the available evidence on the efficacy, safety and tolerability of cannabis products from randomized, double-blind, clinical trials of at least four week's duration for the treatment of fibromyalgia in adults reported that 1 mg nabilone at bedtime was not associated with high to moderate quality evidence for an outcome of efficacy (participant-reported pain relief of > 50%, and Patient Global Impression of Change much or very much improved), tolerability (withdrawal due to adverse events), and safety (serious adverse events) [915]. Low quality evidence was found for nabilone over placebo in pain relief and health-related quality of life, but not in fatigue, and nabilone over amitriptyline in improving sleep quality but not for pain and health-related quality of life. Non-serious adverse events associated with nabilone use included dizziness/drowsiness, dry mouth and vertigo and the incidence of non-serious adverse events with nabilone was higher compared with placebo or amitriptyline.

4.8.4 Muscular pain

Muscular pain affects a large share of the population and is a major clinical problem [916, 917]. Findings from pre-clinical studies using two animal models of acute muscle pain suggest that both systemic (0.3 – 5 mg/kg i.p.) and local administration (0.0125 – 0.1 mg/kg i.m.) of THC is associated with a dose-dependent reduction in frequency of paw shaking and a reduction in time spent in nocifensive behaviour following a noxious muscular stimulus [916]. Differences in the types of cannabinoid receptors engaged were observed according to the route of administration: systemic administration of THC was associated with engagement of CB_1 and/or CB_2 receptors, while local administration of THC in the paw was predominantly associated with engagement of CB_2 receptors [916]. No human experimental or clinical studies exist with cannabinoids for muscular pain.

4.8.5 Osteoporosis

Osteoporosis is a disease characterized by reduced bone mineral density and an increased risk of fragility fractures [918]. 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 [919].

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 [20, 920, 921]. In fact, it appears that CB_1 receptors are expressed more abundantly in skeletal sympathetic nerve terminals in close proximity to osteoblasts [922]. Besides the receptors, the endocannabinoids 2-AG and anandamide have been detected in mouse trabecular bone and in cultures of mouse osteoblasts and human osteoclasts [921, 923, 924]. Taken together, these findings suggest the existence of a functional ECS in bone.

The role of the ECS in bone physiology has been investigated using mice carrying genetic deletions of either the *CNR1* or *CNR2* 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 [20]. 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 [920, 922]. Loss of CB_1 receptor function was associated with protection from ovariectomy-induced bone loss [920]. In addition, antagonism of CB_1 and CB_2 receptors prevented ovariectomy-induced bone loss *in vivo* [920].

A subsequent study by the same group reported that CB_1 knockout mice had increased peak bone mass but eventually developed age-related osteoporosis [918]. 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 [918]. 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 [922]. 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.

Another pre-clinical study in younger and older rats reported that blockade of CB_1 receptor activity, by administration of rimonabant, had differential effects on glucocorticoid-induced cortical bone thickness and mean trabecular bone density [925]. In young rats, rimonabant attenuated the osteoporotic effects of chronic glucocorticoid treatment whereas in older rats, the opposite effect was noted. Furthermore, the findings from this study further support the idea that the CB_1 receptor plays an age-related differential role in bone turnover processes.

In mice, activation of CB_1 receptors by THC has been shown to significantly slow bone elongation and possibly overall body size, at least in female adolescent mice [926]. The concentration of systemic THC administered in the mice (5 mg/kg/day) was reported to be similar to that described for human daily cannabis smokers.

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 [388]. No such effect was observed for cortical bone.

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 [927]. These deficits were associated with increased numbers of osteoclasts and decreased numbers of osteoblast precursors. 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* [927]. 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 [928]. Furthermore, in contrast to the study by Ofek [927], 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 [929]. 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 [929]. Conversely, results from *in vitro* studies suggested that CB_2-selective agonists significantly increased osteoclast formation and osteoclast size [929]. 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 [930-932].

4.9 Other diseases and symptoms

4.9.1 Movement disorders

The individual components of the ECS are particularly abundant in areas of the brain that control movement, such as the basal ganglia [933]. Motor effects generally arise as a consequence of changes in ECS activity, with activation of the CB_1 receptor typically resulting in inhibition of movement [933]. A number of studies have reported changes in CB_1 receptor levels and CB_1 receptor activity in motor diseases such as Parkinson's disease (PD) and Huntington's disease (HD) [934-937], and the findings from such studies suggest a complex link between the ECS and the pathophysiology of these and other neurological diseases.

A systematic review of the efficacy and safety of cannabinoids in movement disorders such as HD, PD, cervical dystonia and TS suggests that cannabinoids are either probably ineffective or of unknown efficacy and that the risks and benefits of cannabinoid treatment should be carefully weighed [671]. In addition, comparative efficacy of cannabinoid vs. other therapies is unknown for these indications [671].

4.9.1.1 Dystonia

- ***Evidence from limited pre-clinical studies suggests that a synthetic CB_1 and CB_2 receptor agonist may alleviate dystonia-like symptoms, and CBD delays dystonia progression.***
- ***Evidence from a limited number of case studies and small placebo-controlled or open-label clinical trials suggests improvement in symptoms of dystonia with inhaled cannabis, mixed effects of oral THC, improvement in symptoms of dystonia with oral CBD, and lack of effect of nabilone on symptoms of dystonia.***

Dystonia involves overactivity of muscles required for normal movement, with extra force or activation of nearby but unnecessary muscles, and is often painful in addition to interfering with function [938]. Dystonia can be primary, including torticollis and blepharospasm/orofacial dyskinesias or dystonias (Meige syndrome) or part of another condition such as HD, and tardive dyskinesia after dopa-blocking drugs [938].

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 receptor agonist WIN 55,212-2 [939]. 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 [939]. A follow-up study by the same group confirmed the anti-dystonic efficacy of WIN 55,212-2 and also showed that CBD delayed the progression of dystonia, but only at a very high dose [940]. 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 [941].

Clinical data
While anecdotal reports suggest cannabis may alleviate symptoms associated with dystonia in humans [248], no properly controlled clinical studies of cannabis to treat dystonia have been published.

One case-study reported improvement in torticollis after smoking cannabis [942]. Another case study reported improvement in a patient with central thalamic pain and right hemiplegic painful dystonia who smoked one joint in the morning once per week for three weeks [943]. Following smoking, the patient reported complete pain relief and relief of paresthesia and marked improvement in dystonia with improved ability to write and take a few steps without support. Pain relief appeared to persist for up to 48 h after each episode of cannabis smoking. No tolerance to the effects of cannabis was noted and the patient discontinued opioid analgesic therapy. Another case report of a 25-year-old patient using cannabis for generalized dystonia secondary to Wilson's disease reported that smoking 3 or 4 g of cannabis per day was associated with significant improvement in his dystonia [248]. Physician observation supported the patient's claims: cannabis decreased the score on the *Burke-Fahn-Marsden* dystonia rating scale and the disability scale by 50% each. Therapeutic effects did not appear to persist beyond each 24 h period, requiring the patient to administer cannabis daily.

A placebo-controlled, single-dose trial with 5 mg of Δ^9-THC administered orally 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 [250]. The therapeutic effect persisted until 2 h after intake, with a progressive return to baseline values after 5 h.

An eight-week, phase IIa, cross-over, randomized, placebo-controlled trial of dronabinol (15 mg/day) in nine patients with cervical dystonia reported a lack of effect of dronabinol compared to placebo on any outcome measure (Toronto Western Spasmodic Torticollis Rating Scale – TWSTRS, VAS of pain, global impression of change) [244]. Most subjects experienced an adverse event, none of which was deemed serious. Adverse events with dronabinol included light-headedness, sleepiness, dry mouth, blurred vision, bitter-taste and vertigo, and were deemed mild.

Another case-study reported that dronabinol (2.5 mg, b.i.d. initially, then 5 mg, b.i.d.) was associated with improvement in dystonia in a patient with MS, paroxysmal dystonia, complex vocal tics, and cannabis dependence (minimum daily consumption of five cannabis joints) and who had previously reported symptom improvement after smoking cannabis [247]. The patient also reported a significant reduction in cannabis craving, an improvement in quality of sleep, decreased vocalizations, decreased anxiety and decreased frequency of paroxysmal dystonia with dronabinol.

A six-week, open-label, pilot trial of five patients taking 100 to 600 mg/day of CBD reported modest dose-related improvements in dystonic movements in all study subjects, but a worsening of tremor and hypokinesia in two patients with co-existing PD administered doses of CBD > 300 mg/day [261]. Side effects of CBD were mild and included hypotension, dry mouth, psychomotor slowing, light-headedness, and sedation.

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 [253].

4.9.1.2 Huntington's disease

- ***Evidence from pre-clinical studies reports mixed results with THC on Huntington's disease (HD)-like symptoms.***
- ***Limited evidence from case studies and small clinical trials is mixed and suggests a lack of effect with CBD, nabilone and nabiximols, and a limited improvement in HD symptoms with smoked cannabis.***

Pre-clinical and human experimental data

Results from studies carried out in animal models of HD as well as post-mortem studies carried out in deceased 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 [934, 944-953]. *In vivo* positron emission topography (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 [954]. Additional pre-clinical and post-mortem studies in deceased 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 [949, 955]. Thus, a significant amount of pre-clinical evidence and some limited clinical evidence suggests that changes in the ECS are tightly linked to the pathophysiology of HD [949, 952-954].

One pre-clinical study in a mouse model of HD reported no beneficial effects of Δ^9-THC (10 mg/kg/day) [956], 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 [951]. Another pre-clinical animal study in a rat model of HD showed that CB_2 receptor activation was associated with reduction in inflammatory markers associated with an HD-like phenotype and protection of striatal projection neurons [957]. A pre-clinical study has also reported that a restricted population of CB_1 receptors selectively located on glutamatergic terminals in corticostriatal projections may play a potentially protective role in attenuating excitotoxic damage associated with excessive glutamate release in HD, raising the possibility that selective targeting of this receptor population may help attenuate neurodegeneration in patients with HD [958].

Clinical data

The results from single-patient case studies are mixed. In one study, daily doses of 1.5 mg nabilone increased choreatic movements [256], 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. [959].

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 CBD did not report improvement in symptoms associated with HD [258]. A randomized, double-blind, placebo-controlled, crossover pilot study found little or no beneficial effect of 1 or 2 mg nabilone over placebo in 37 patients with HD [245]. 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.

A more recently published 12-week, double-blind, randomized, placebo-controlled, cross-over, pilot trial examining the safety and tolerability of nabiximols in HD reported no significant differences on motor, cognitive, behavioural or functional outcomes associated with the use of nabiximols compared to placebo in 26 HD patients with the exception of an increased incidence of dizziness and reduced attention in the treatment group [241]. Limitations of the study include lack of power to determine if nabiximols is effective and safe in the long-term or if tested in larger populations. In addition, the authors suggest that the observed lack in efficacy may have been explained, at least in part, by treatment during the later stage of HD and that treatment at an earlier stage should be explored in future clinical studies.

4.9.1.3 Parkinson's disease

- ***The evidence from a limited number of pre-clinical, case, clinical and observational studies of certain cannabinoids for symptoms of Parkinson's disease (PD) is mixed.***
- ***One case study of smoked cannabis suggests no effect while an observational study of smoked cannabis suggests improvement in symptoms.***
- ***One small clinical study of nabilone suggests improvement in symptoms, while another clinical study of an oral cannabis extract (THC/CBD) and a clinical study with CBD suggest no improvement in symptoms.***

A patient survey distributed among 630 patients attending a movement disorders clinic reported that out of the 339 respondents, 25% had used cannabis with 31% reporting benefit in rest tremor, 45% in bradykinesia, and 14% in dyskinesia [960].

Pre-clinical and human experimental data

Endocannabinoid ligands, their synthesizing and degrading enzymes, and cannabinoid-activated receptors are highly abundant in the basal ganglia, the brain structures primarily affected in PD [933]. Newly diagnosed PD patients and those undergoing PD medication washout were reported to have more than double the level of anandamide in their CSF 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 [961]. 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 [961, 962]. Together, these studies suggest a complex link between the pathophysiology of PD and changes in the ECS.

Results from some animal studies suggest cannabinoid receptor agonists induce hypokinesia and thus are reported to be unlikely as suitable first-line treatments for PD [933, 963]. On the other hand, cannabinoid-induced hypokinesia could be useful in attenuating the dyskinesia observed in PD patients on long-term levodopa treatment [963]. Other animal studies suggest CB_1 receptor antagonism (via treatment with rimonabant) partially attenuates hypokinesia associated with nigral cell death and promotes dopaminergic neuron survival in the substantia nigra pars compacta through an increase in astrocyte cell density [964, 965]. However, this beneficial effect of CB_1 receptor antagonism could not be replicated in a small clinical study [251]. Given the current level of evidence for cannabinoids in the treatment of PD, it would appear that cannabinoid-based neuroprotective therapy for PD would need to be based on an adequate combination of selected compounds that confer antioxidant effects (e.g. through CB-receptor independent mechanisms) such as through activation of the nuclear PPAR receptor family, CB_2 receptor activation and control of inflammation, and CB_1 receptor antagonism to improve akinesia and reduce motor inhibition [966]. Combining a cannabinoid with anti-inflammatory and anti-oxidant properties (CBD) with a cannabinoid having mixed CB_1 antagonist/CB_2 agonist properties as well as anti-oxidant effects (THCV) may possibly hold some therapeutic potential, but much further research is required [966].

Clinical data

The results of clinical trials examining the role of cannabinoids (smoked cannabis, nabilone, CBD, rimonabant and a standardized oral cannabis extract) in the treatment of PD are mixed.

One case 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 [259].

An open-label, observational study evaluated the clinical effect of smoked cannabis on motor and non-motor symptoms in 22 patients with PD who were using cannabis daily for at least two months with no major side effects [242]. Patients were asked to smoke their regular dose of cannabis (500 mg) and 30 min later, the motor and non-motor test batteries were administered and scores recorded by two clinicians. The mean total score on the motor Unified Parkinson's Disease Rating Scale (UPDRS) score improved significantly after cannabis exposure, from a score of 33 at baseline to a score of 23 after cannabis consumption ($p < 0.001$). Significant improvement was also noted in tremor, rigidity, bradykinesia, sleep and pain but none on posture. All patients were concomitantly taking other PD medications including levodopa, amantadine, rasagiline, selegiline, acetylcholinesterase inhibitor, and others. No serious adverse events were noted. Main self-reported adverse effects of long-term cannabis smoking were somnolence, drowsiness, palpitations, and bad taste. Study limitations included open-label design and short study period.

An exploratory, randomized, double-blind, placebo-controlled clinical study of antagonists to the neurokinin B, neurotensin and CB_1 receptor (rimonabant) on the severity of motor symptoms and levodopa-induced dyskinesias after a single dose of levodopa in 24 patients with PD showed that at the dose used, all three drugs were well tolerated and could not improve Parkinsonian motor disability [251]. Doses for neurokinin B, neurotensin and CB_1 receptor antagonists were 180 mg, 200 mg, and 20 mg respectively. Each drug was administered once daily, 1 h before the administration of levodopa for 9 (neurokinin, neurotensin B) or 16 days (rimonabant).

A small randomized clinical trial of nabilone (0.03 mg/kg) in seven patients with PD found that nabilone reduced levodopa-induced dyskinesia [254].

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 CBD per capsule, b.i.d.; maximum daily dose 0.25 mg/kg Δ^9-THC) did not produce any pro- or anti-parkinsonian action [249].

Lastly, an exploratory double-blind clinical trial of 21 patients with PD (without dementia or comorbid psychiatric conditions) assessed the motor and general symptoms score (UPDRS), functioning/well-being and QoL (39-item Parkinson Disease Questionnaire, PDQ-39) and possible neuroprotective effects (plasma brain-derived neurotrophic factor (BDNF) and proton magnetic resonance spectroscopy, H^1-MRS) following treatment with placebo or CBD (75 mg or 300 mg/day) for six weeks [243]. No statistically significant differences were observed between placebo and all CBD doses for UPDRS scores, plasma BDNF levels or H^1-MRS measures. However, the 300 mg CBD dose was associated with a statistically significant difference in mean total scores from placebo in the PDQ-39 suggesting that the 300 mg daily CBD dose is associated with an improvement in QoL measures in PD patients with no psychiatric comorbidities.

4.9.1.4 Tourette's syndrome

- ***The limited evidence from small clinical studies suggests that oral THC improves certain symptoms of Tourette's syndrome (TS) (tics).***

Anecdotal and case-reports have suggested amelioration of symptoms associated with TS when smoking cannabis [257, 260]. In addition, 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 TS showed plasma concentration-related improvements in control of motor and vocal tics and obsessive-compulsive behaviour, with no serious side effects; although transient, mild side effects (e.g. headache, nausea, ataxia, fatigue, anxiety) were noted in five patients [255]. 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 TS. 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 [252]. 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 TS concluded that there was insufficient evidence to support the use of cannabinoids in treating tics and obsessive compulsive behaviour in persons suffering from TS [246].

However, a more recent systematic review and meta-analysis of 28 RCTs (N = 2 454 participants) of cannabinoids (i.e. smoked cannabis, nabiximols, nabilone, dronabinol, CBD, THC, levonontradol, ajulemic acid) using the GRADE approach concluded that based on two small placebo-controlled studies of orally-administered THC in capsule form in the treatment of symptoms associated with TS, oral THC may be associated with significant improvement in tic severity in patients with TS [179].

4.9.1.5 Spinocerebellar ataxias

There is emerging evidence of a role for the ECS in the pathophysiology of spinocerebellar ataxias [967, 968]. Post-mortem studies of cerebellar samples collected from deceased patients with hereditary autosomal dominant ataxias revealed significant increases in the protein expression levels of FAAH and MAGL in the Purkinje cells in the cerebellar granular layer, in neurons of the dentate nucleus, and in cerebellar white matter compared to controls [968]. In another study, the protein expression levels of the CB_1 and CB_2 receptors in these same areas of the cerebellum were also found to be significantly increased compared to controls [967]. These studies suggest an increase in the expression levels of a number of components of the ECS in cerebellar areas associated with hereditary autosomal dominant ataxias.

4.9.2 Glaucoma

- ***The limited evidence from small clinical studies suggests oral administration of THC reduces intra-ocular pressure (IOP) while oral administration of CBD may, in contrast, cause an increase in IOP.***

Glaucoma is a multi-factorial disease characterized by the progressive degeneration of the optic nerve and the death of retinal ganglion cells ultimately leading to irreversible blindness [969]. Increased IOP has been implicated in the pathophysiology of glaucoma; however, inadequate blood supply to the optic nerve, oxidative damage, and apoptosis of retinal ganglion cells are also contributing factors [390, 969-971]. An ECS exists in a number of ocular tissues, and post-mortem studies have detected decreased levels of endocannabinoids in such tissues taken from deceased glaucoma patients [972].

Ocular (as well as systemic) administration of cannabinoids typically lowers IOP by up to 30% (see [390] 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 [973-977].

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 [978].

A well-controlled pilot clinical 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 [389]. A single sub-lingual dose of 20 mg CBD (co-administered with approx. 1 mg Δ^9-THC) had no effect, while a single sub-lingual dose of 40 mg of CBD (co-administered with ~ 2 mg Δ^9-THC) caused a significant transient increase in IOP 4 h after administration. 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 standard medications or surgery [391]. Some patients appeared to develop tolerance to the IOP-lowering effects of Δ^9-THC, and almost half discontinued treatment due to Δ^9-THC-associated side effects (e.g. dizziness, dry mouth, sleepiness, depression, confusion). 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 [390, 979-988].

In conclusion, while smoking or eating cannabis (or oral Δ^9-THC) has been reported to reduce IOP [989-991], cannabinoid-based therapy appears to be limited by the short duration of cannabinoid action (3 – 4 h) and unwanted physical and psychotropic effects.

4.9.3 Asthma

- ***The limited evidence from pre-clinical and clinical studies on the effect of aerosolized THC on asthmatic symptoms is mixed.***
- ***Inhalation of lung irritants generated from smoking/vapourizing cannabis may worsen asthmatic symptoms.***

There is some historical and anecdotal evidence for cannabis as a treatment for asthma [992]. In terms of pre-clinical data, there is some evidence suggesting a role for the ECS in regulating bronchial smooth muscle tone [993] and studies with animals using classical and synthetic cannabinoids suggest a possible role for cannabinoid-based compounds in the treatment of asthma [994-996].

Early clinical studies demonstrated significant decreases in airway resistance and increases in specific airway conductance in healthy, habitual cannabis smokers shortly after smoking cannabis [997, 998]. This effect has been largely attributed to the bronchodilatory properties of Δ^9-THC [999]. 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 [1000-1002], cannabis smoke contains noxious gases and particulates that irritate and damage the respiratory system [999]; hence, it is likely not a viable long-term therapy for asthma. A number of studies have also reported hypersensitivity reactions, including asthmatic attacks in response to inhalation of cannabis smoke [365, 366].

Importantly, therefore, 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 [1003, 1004]. In another study, 5 to 20 mg of aerosolized Δ^9-THC rapidly and effectively increased airway conductance in healthy subjects, but caused either bronchodilatation or bronchoconstriction in asthmatics [1005]. Oral administration of 10 mg Δ^9-THC or 2 mg nabilone did not produce clinically significant bronchodilatation in patients with reversible airways obstruction [992, 1006, 1007].

4.9.4 Hypertension

CB_1 receptors are expressed on various peripheral tissues including the heart and vasculature, and CB receptor agonists and endocannabinoids decrease arterial blood pressure and cardiac contractility (reviewed in [1008]).

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 [1009]. 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.

4.9.5 Stress and 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, PTSD, 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.

The endocannabinoid system, stress and psychiatric disorders

Increasing evidence suggests an important role for the ECS in the regulation of stress, mood, and psychiatric disorders [167, 1010, 1011]. Pharmacological or genetic disruption of endocannabinoid signaling in animals produces a neurobehavioural response that mimics the classical stress response including activation of the hypothalamic-pituitary-adrenal (HPA) axis, increased anxiety, suppressed feeding behaviour, reduced responsiveness to rewarding stimuli, hypervigilance and arousal, enhanced grooming behaviour and impaired cognitive flexibility [167].

In animal models of *acute* stress, exposure to a variety of acute psychological stressors generally causes a rapid reduction in brain levels of anandamide which is accompanied by a number of behavioural and physiological responses including an increase in anxiety, increased activity of the HPA axis, a decrease in neurogenesis, decreased ability to extinguish fearful memories, and anhedonia, all of which are also hallmarks of mood disorders [167, 1011]. *Chronic* stress also generally appears to produce reductions in anandamide similar to those seen with acute stress [167]. However, in contrast to the situation with anandamide, acute and chronic stress cause a protracted increase in brain 2-AG levels that is preceded by increases in corticosterone resulting from increased HPA axis activity [167]. Furthermore, elevations in brain 2-AG levels are associated with HPA axis response termination, HPA axis habituation, modulation of synaptic plasticity, decreased memory retrieval and a decrease in pain [167]. The ECS therefore appears to be both a target and a regulator of stress-induced activation of the HPA axis [167].

Endocannabinoids appear to reduce behavioural signs of anxiety, especially under stressful, aversive or otherwise challenging conditions [167]. Elevation of both 2-AG and anandamide signaling attenuates stress-induced anxiety, though apparently through different mechanisms [167, 1010]. There is also increasing evidence pointing to a role for the ECS in facilitating the extinction of emotionally aversive memories [167, 1010]. In humans, experimental studies employing pharmacological means of disrupting endocannabinoid signaling through the use of the CB_1 receptor antagonist/inverse agonist rimonabant suggest that impairments in endocannabinoid signaling result in increased sensitivity to the effects of stress including anxiety and anhedonia [167, 1010]. Both depression and PTSD have been associated with reduced levels of circulating endocannabinoids [167, 1010].

Taken together, the weight of the evidence suggests that the ECS functions as a homeostatic mechanism for buffering stress, inhibiting unnecessary HPA axis activation and promoting the recovery of the HPA axis once the stressful stimulus has passed [1010, 1011]. Dysfunction of the ECS both increases sensitivity to stress and prolongs maladaptive responses to stress in the absence of any further stress stimulus [1010, 1011]. Importantly, chronic stress appears to reduce the ability of the ECS to buffer stress effectively and can contribute to precipitation of psychopathology including anxiety and depression [1010, 1011]. Pharmacological interventions that function to *raise* endocannabinoid tone such as inhibition of the endocannabinoid degradative enzymes FAAH and MAGL appear to have anxiolytic and anti-depressive effects, at least in animal models of anxiety and depression [167, 177, 1011]. Emerging evidence suggests substrate-selective inhibition of COX-2 also increases brain endocannabinoid levels and may have anxiolytic effects [167, 1012, 1013].

4.9.5.1 Anxiety and depression

- ***Evidence from pre-clinical and clinical studies suggests that THC exhibits biphasic effects on mood, with low doses of THC having anxiolytic and mood-elevating effects and high doses of THC having anxiogenic and mood-lowering effects.***
- ***Limited evidence from a small number of clinical studies of THC-containing cannabis/certain prescription cannabinoids suggests that these drugs could improve symptoms of anxiety and depression in patients suffering from anxiety and/or depression secondary to certain chronic diseases (e.g. patients with HIV/AIDS, MS, and chronic neuropathic pain).***
- ***Evidence from pre-clinical studies suggests that CBD exhibits anxiolytic effects in various animal models of anxiety, while limited evidence from clinical studies suggest CBD may have anxiolytic effects in an experimental model of social anxiety.***
- ***Limited evidence from some observational studies also suggests that cannabis containing equal proportions of CBD and THC is associated with an attenuation of some perturbations in mood (anxiety/dejection) seen with THC-predominant cannabis in patients using cannabis for medical purposes.***

As mentioned above, cannabis consumption, especially cannabis containing mainly THC, appears to dose-dependently affect anxiety behaviours, with low doses (of THC) being potentially anxiolytic and high doses (of THC) either ineffective or potentially anxiogenic [177]. While acute consumption of higher doses of THC-predominant cannabis can, in some individuals and in certain novel or stressful environments, trigger significant anxiety which can resemble a panic attack, long-term cannabis users report reductions in anxiety, increased relaxation, and relief from tension [191]. 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 [1014]. However, the study suffered from a number of serious drawbacks and should be interpreted with caution. Other epidemiological studies suggest the opposite [1015, 1016]. Daily users may also report anxiety reduction that may actually be relief of withdrawal symptoms associated with CUD. Furthermore, social anxiety disorder appears particularly related to CUD and according to at least one study, some people with social anxiety may come to rely on cannabis to help them cope in social situations, continuing to use cannabis despite experiencing negative consequences related to its use and thereby developing CUD [1017].

Pre-clinical studies

Pre-clinical (and clinical) evidence indicates important roles for the ECS in both anxiety and mood disorders. Results from animal studies suggest low doses of CB_1 receptor agonists reduce anxiety-like behaviour and increase anti-depressant-like responses [1018, 1019]. CB_1 receptor agonists appear to enhance central serotonergic and noradrenergic neurotransmission similar to the actions of anti-depressant medications [1020, 1021]. 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 depressive-like symptoms or depression [189, 1020, 1022, 1023]. Suppression of endocannabinoid signalling is sufficient to induce a depressive-like state both in animals and in humans (reviewed in [1024]). Furthermore, basal serum concentrations of both anandamide and 2-AG have been found to be significantly reduced in women with major depression [1025]. These findings suggest proper endocannabinoid tone plays an important role in regulating mood.

Clinical and observational data for cannabis and THC

While the routine use of THC-predominant cannabis or prescription cannabinoid medications containing primarily THC (dronabinol) to treat primary anxiety or depression should be viewed with caution, and especially discouraged in patients with a history of psychotic disorders (see **Section 7.7.3.2**), 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 [1026]. It is important to note that 47% of those surveyed reported deterioration in memory. In another within-subject, double-blind, placebo-controlled, clinical 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" [298]. 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 MS [1027]. Improvements in anxiety or depression were equally noted in a clinical study of patients suffering from chronic neuropathic pain who smoked cannabis [59]. 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 [1023, 1028]. For additional information on the association between cannabis and anxiety and depression please see **Section 7.7.3.1** and between cannabis and suicide, please see **Section 7.7.3.3.**

Cannabidiol

Pre-clinical data

More than 30 pre-clinical studies have been carried out examining the anxiolytic effects of CBD in a variety of animal models of various types of anxiety disorders including generalized anxiety disorder, social anxiety disorder, panic disorder, obsessive-compulsive disorder and PTSD [171]. In general, the findings from these pre-clinical studies support the anxiolytic effects of CBD [171]. In addition, CBD also appears to have panicolytic and anti-compulsive effects and decreases autonomic arousal and conditioned fear expression. CBD also appears to enhance fear extinction, promote reconsolidation blockade, and prevent long-term anxiogenic effects of stress [171]. While the exact anxiolytic mechanism of action of CBD is unclear, one proposed molecular target of CBD is the $5\text{-}HT_{1A}$ receptor [171].

Clinical data

Findings from functional neuroimaging studies suggest differential cerebral blood flow effects associated with administration of CBD compared with those seen with placebo or THC [171]. 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 [1029]. 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 [126]. In contrast, 10 mg of Δ^9-THC increased anxiety at baseline or in response to anxiogenic stimuli, and the brain regions affected by Δ^9-THC differed from those affected by CBD [126]. 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 [171, 1030, 1031]

At least 10 clinical studies have examined the acute anxiolytic properties of CBD [171]. Indeed, increasing evidence suggests pure CBD, at doses of several hundred milligrams (i.e. 300 – 600 mg, p.o.) may be effective in decreasing acute, *experimentally-induced* social anxiety in the clinic, although the extent to which CBD (at the relatively lower concentrations commonly found in THC-predominant cannabis) is able to achieve anxiolysis either in an experimental, or more importantly in a real-life setting remains uncertain. While clinical findings related to the anxiolytic effects of CBD are currently limited to acute experimental models of social anxiety [171], one observational study of 100 patients who self-reported using cannabis for medical purposes for conditions such as MS, chronic pain, nausea, cancer and psychological problems, reported that those who used cannabis with cannabinoid concentrations of 6% THC and 7.5% CBD (i.e. “low THC” condition) reported significantly less anxiety and dejection (i.e. feeling down, sad, depressed), but also reported less appetite stimulation, compared to those who reported using “high THC” (19% THC, <1% CBD) or “medium THC” (12% THC, <1% CBD) strains [118].

4.9.5.2 Sleep disorders

- ***Human experimental data suggests cannabis and THC have a dose-dependent effect on sleep—low doses appear to decrease sleep onset latency and increase slow-wave sleep and total sleep time, while high doses appear to cause sleep disturbances.***
- ***Limited evidence from clinical studies also suggests that certain cannabinoids (cannabis, nabilone, dronabinol, nabiximols) may improve sleep in patients with disturbances in sleep associated with certain chronic disease states.***

Human experimental data

There is some evidence from experimental studies to suggest a role for the ECS in the regulation of sleep. Subjects deprived of sleep for a 24 h period had increased levels of OEA, a natural analogue of anandamide, in their CSF but not in serum, whereas levels of anandamide were unchanged [1032]. Recent studies have shown daily variation in 2-AG concentrations that are amplified under sleep restriction [1033]. 2-AG levels appear lowest around midsleep and increase continually across the morning, peaking in the early to mid-afternoon with concentrations of 2-oleoylglycerol (2-OG), a structural analogue of 2-AG, following a similar pattern [1034]. In rats, both acute and sub-chronic administration of anandamide induces sleep [1035]. Cannabis containing mainly THC, as well as Δ^9-THC itself are known to have a number of effects on sleep in humans, which may be dose-dependent (i.e. low doses appearing beneficial on some measures of sleep, high doses causing sleep disturbances). In general, it appears that at low doses these substances (THC-predominant cannabis, THC) decrease sleep onset latency and are associated with greater ease in getting to sleep whereas the opposite is true at high doses; there is a consistent reduction in total rapid eye movement (REM) sleep and REM density (reviewed in [209, 340]). Low doses of THC also increase beneficial slow-wave sleep (critical for learning, memory consolidation, and memory retrieval) and total sleep time, while high doses decrease slow-wave sleep [340]. Furthermore, due to the long half-life of THC, sedative effects may typically persist into the day following administration [209].

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 [340, 1036]. Trouble getting to sleep, nightmares and/or strange dreams, and night sweats were frequently cited symptoms associated with cannabis withdrawal [342]. These sleep disturbances progress over the first two weeks of abstinence [1037]. Furthermore, sleep disturbances resulting from abrupt discontinuation of cannabis use may trigger users to relapse [403, 1037]. The symptoms observed during abstinence from cannabis may alternatively reveal a pre-existing sleep disorder masked by the drug.

Clinical data

A systematic review and meta-analysis of 28 RCTs (N = 2 454 participants) of cannabinoids (i.e. smoked cannabis, nabiximols, nabilone, dronabinol, CBD, THC, levonontradol, ajulemic acid) using the GRADE approach reported that there was some evidence that cannabinoids may improve sleep (insomnia, sleep quality, sleep disturbance) [179].

Indeed, 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, MS, ALS, SCI, RA, fibromyalgia, inflammatory bowel disease (IBD), MS-associated bladder dysfunction, PTSD, chemosensory alterations and anorexia-cachexia associated with advanced cancer [59, 184, 185, 223-225, 298, 383, 578, 597, 611, 612, 642, 697, 704, 708, 715, 716, 822, 838]. 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 a number of these studies are presented below.

Dronabinol

A four-week, randomized, double-blind, crossover pilot clinical study of 19 patients suffering from ALS taking 2.5 – 10 mg per day of dronabinol reported improvements in sleep [708]. Two clinical 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 consumed) produced improvements in mood and sleep in patients with HIV/AIDS-associated anorexia-cachexia [223, 224]. A clinical 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 [298]. A two-centre, phase II, randomized, double-blind, placebo-controlled, 22-day pilot clinical 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 [611]. An open-label pilot study of add-on oral THC (25 mg/mL THC in olive oil; 2.5 mg THC b.i.d., maximal daily dose 10 mg THC) in patients with chronic PTSD reported improvement in sleep quality and frequency of nightmares [571].

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 [822]. 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 [612]. 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 [597]. Two clinical studies looked at nabilone for sleep disturbances in PTSD. An open-label, non-placebo-controlled trial of nabilone for PTSD reported that nabilone treatment was associated with an improvement in sleep time, cessation or lessening of nightmare severity, and cessation of night sweats [578]. Dosing of nabilone was 0.5 mg, 1 h prior to bedtime; effective dose range was 0.2 mg to 4 mg nightly with all doses kept below 6 mg daily. A subsequent preliminary, randomized, double-blind, placebo-controlled cross-over clinical study of 10 Canadian male military personnel with PTSD who were not responsive to conventional treatment and who continued to experience trauma-related nightmares, received 0.5 mg nabilone or placebo and titrated to the effective dose (i.e. nightmare suppression) or to a maximum daily dose of 3 mg nabilone [1038]. Average dose achieved for nabilone was 2 mg/day. Treatment arms lasted for seven weeks each, with a two-week washout period in between. Half (50%) of the subjects reported a significant improvement in nightmare suppression on nabilone, while only 11% of subjects reported improvement with placebo.

Smoked cannabis

Surveys carried out among patients suffering from MS reported cannabis-associated improvements in sleep in this patient population [225, 226]. Reported dosages of smoked cannabis varied from a few puffs, to 1 g or more, at a time [225]. 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 [184]. A cross-sectional survey of 291 patients with IBD (Crohn's disease or ulcerative colitis) reported that one of the reasons patients used cannabis was to improve sleep [185]. 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 [59].

Orally administered prescription cannabinoid medications (Cannador and nabiximols)
A double-blind, placebo-controlled, phase III study, involving patients with stable MS (i.e. **MUSEC** study) reported that a 12-week treatment with an oral cannabis extract ("Cannador") (2.5 mg Δ^9–THC and 0.9 mg CBD/dose) was associated with a statistically significant improvement in sleep compared to placebo [697]. 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 clinical 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 SCI [642, 715, 716]. A preliminary clinical study assessing the effectiveness of nabiximols in pain caused by RA reported a modest, but statistically significant, analgesic effect and consequent improvement in quality of sleep [383]. 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 nabiximols 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 nocturia and improvement in patient self-assessment of sleep quality [704].

The 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) [838].

4.9.5.3 Post-traumatic stress disorder

- ***Pre-clinical and human experimental studies suggest a role for certain cannabinoids in alleviating post-traumatic stress disorder (PTSD)-like symptoms.***
- ***However, while limited evidence from short-term clinical studies suggests a potential for oral THC and nabilone to decrease certain symptoms of PTSD, there are no long-term clinical studies for these preparations or any clinical studies of smoked/vapourized cannabis for PTSD.***
- ***Limited evidence from observational studies suggests an association between herbal cannabis use and persistent/high levels of PTSD symptom severity over time.***
- ***There is limited evidence to suggest an association between PTSD and CUD.***

PTSD is a psychiatric disorder of significant prevalence and morbidity [1039]. In the overall population, more than two thirds of individuals may experience a serious traumatic event at some point in their lifetime [1039]. 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 [1040]. 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 [578]. Sleep disturbance also occurs in up to 90% of cases [1038]. Patients with PTSD are also at risk for other psychological disorders, including but not limited to generalized anxiety disorder, major depressive disorder, and substance use disorder as well as physical problems including chronic pain, hypertension, and asthma [1041]. There appears to be a link between exposure to a traumatic event and cannabis use, especially in military veterans, and research suggests that individuals with PTSD may be particularly likely to use cannabis specifically to alleviate symptoms of PTSD and associated distress [1039, 1041, 1042]. There is also evidence to suggest that particular symptoms and correlates of PTSD including anxiety, stress, insomnia and depression are among the most frequently cited reasons for cannabis use [1042]. Despite much anecdotal evidence suggesting the benefits of cannabis use to treat PTSD, there is a lack of standardized large-scale controlled trials to make any firm conclusions regarding the efficacy or safety of cannabis for the treatment of PTSD [1043].

While affected individuals may use cannabis to cope with negative internal states, there is increasing evidence that these individuals may also experience more problematic cannabis use as well as heightened withdrawal and craving when not intoxicated [1042]. Indeed, compared to individuals who do not have PTSD, those who have PTSD (and especially those whose symptoms are severe) report significantly increased use of cannabis to cope and to sleep, increased severity of cannabis withdrawal, and experiences of craving related to compulsivity, emotionality, and anticipation, and these findings suggest the existence of a positive feedback loop between PTSD symptomatology and cannabis use [1042, 1044]. In support of these findings, data from the **N**ational **C**omorbidity **S**tudy (**NCS**) has also shown that adults suffering from PTSD were three times more likely to have a diagnosis of cannabis dependence compared to those without PTSD [1045]. In addition, an epidemiological study on the prevalence and correlates of DSM-5 CUD using data from the 2012 – 2013 wave of the **NESARC-III** study reported that past-year CUD was associated with PTSD (adjusted OR (AOR) = 4.3), and that lifetime CUD was also associated with PTSD (AOR = 3.8) [338]. Furthermore, the association between PTSD and past-year CUD increased with increasing severity of CUD (AOR = 2.1, 6.2, and 9.5 for mild, moderate, and severe CUD respectively). Furthermore, a study that examined the prevalence and correlates of 186 patients seeking the use of cannabis for medical purposes for the first time found that patients who screened positive for PTSD had higher percentages of lifetime prescription opioid, cocaine, prescription sedative, and street opioid use (55%, 38%, 41%, and 17% respectively), as well as a higher percentage of recent prescription sedative use (29%) than those patients who screened negative for PTSD [1046].

Role of the endocannabinoid system in PTSD

Increasing evidence suggests an important role for the ECS in PTSD. The ECS has been associated with the regulation of emotional states and cognitive processes, and neuroanatomical studies have detected the presence of ECS 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 implicated in PTSD (reviewed in [1040]). The ECS links stress exposure to changes in synaptic plasticity contributing to activation and feedback regulation of the HPA axis, and facilitates the activation of resilience factors during and/or after stress exposure [1047]. It has been hypothesized that chronic stress creates a “hypocannabinergic state” that results in impaired fear extinction (as is seen in PTSD) and this state can be alleviated with CB_1 receptor agonists [1047]. Fear-conditioning experiments in animals suggest a role for the amygdala-hippocampal-cortico-striatal circuit as a key brain circuit responsible for processing and storing fear-related memories and for coordinating fear-related behaviours [1048]. Additional evidence in humans suggests that PTSD is characterized by over-activity or hyper-responsiveness of the amygdala, with deficient regulation of prefrontal cortical structures as well as abnormal hippocampal and basal ganglia functions [1048]. As 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, the use of certain animal behavioural models to study PTSD is feasible and relevant [1040, 1049].

Pre-clinical data

There is evidence to suggest that the endocannabinoids, anandamide and 2-AG play important roles in the development and function of the PTSD neurocircuit, especially in stress responses [1048]. Impaired CB_1 receptor function has been suggested as a potentially important etiological mechanism of PTSD [1048]. Indeed, 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 [1049-1052]. Conversely, in some cases, CB_1 receptor agonism or increased endocannabinoid-mediated neurotransmission (e.g. via inhibition of FAAH) appear to enhance extinction to some degree [1049, 1052], but further research is required to clarify and substantiate this effect. Studies in animals also show that reduction of endocannabinoid levels (mainly 2-AG but also anandamide) via Dagla gene knockout is associated with increased anxiety, stress and fear responses [1053]. Taken together, the evidence from pre-clinical studies suggests a role for the ECS in the extinction of aversive memories and impairment of memory retrieval. Furthermore, the available evidence raises the possibility that manipulation of the ECS (via inhibition of FAAH, upregulation of DAGL, increased anandamide or 2-AG tone, or even perhaps via administration of CBD) can facilitate disruption of contextual fear memories as well as have anti-anxiogenic effects [1039, 1054]. These may represent potential therapeutic options for the treatment of diseases associated with inappropriate retention of aversive memories or inadequate responses to aversive situations, such as PTSD or phobias [1050], although much additional research is needed.

Human experimental and clinical data

Studies in humans have shown that individuals with PTSD have lower circulating endocannabinoid concentrations and an upregulation of brain CB_1 receptors [1011, 1048, 1055-1057]. In addition, there is evidence to suggest that humans (and mice) carrying a common variant of the *FAAH* gene (C385A; rs325520) conferring decreased FAAH protein stability and increased anandamide signaling showed decreased threat-related amygdala reactivity, increased reward-related ventral striatal reactivity, and enhanced fear extinction [1058, 1059].

A double-blind, placebo-controlled, within-subject clinical study of 16 healthy volunteers looking at the effects of THC on amygdala reactivity to threat found that a 7.5 mg dose of dronabinol (vs. placebo) was associated with a significant reduction in amygdala reactivity to social signals of threat, but did not affect activity in primary visual and motor cortices [1060]. These findings are consistent with evidence suggesting that, at least at low doses, THC may have an anxiolytic effect in central mechanisms of fear behaviours.

In one randomized, double-blind, placebo-controlled, between-subjects clinical study, 29 healthy volunteers (with many having minimal cannabis use) were administered either 7.5 mg dronabinol or placebo 2 h prior to extinction learning following a fear conditioning paradigm [1061]. The study showed that pre-extinction administration of THC facilitated extinction of conditioned fear in healthy human subjects. Limitations of the study include the use of a healthy subject population (results may differ in other populations), and lack of generalizability of the results to a population of chronic cannabis users. The authors suggested that this study was the first in humans to demonstrate the feasibility of pharmacological enhancement of extinction learning, though they cautioned that additional development and clinical testing are warranted.

A follow-up study by the same group using functional magnetic resonance imaging (fMRI) in a randomized, double-blind, placebo-controlled, between-subjects study in 28 healthy volunteers (with many having minimal cannabis use) showed that study subjects who received 7.5 mg dronabinol (vs. placebo) showed decreased reactivity in the amygdala and increased activation of the ventromedial prefrontal cortex and the hippocampus to a previously extinguished conditioned stimulus during extinction memory recall [1062].

Another randomized, double-blind, placebo-controlled, between-subjects clinical study of 48 healthy participants found that CBD enhanced the consolidation of explicit fear extinction in humans [1063]. In this study, participants were administered either 32 mg (a sub-anxiolytic dose) of inhaled CBD *prior* to extinction, 32 mg of CBD *following* extinction, or placebo. CBD administered *after* extinction learning was associated with an attenuation of explicit fearful responding during recall and reinstatement. However, there was a trend for reduction in reinstatement in subjects administered CBD either before *or* after extinction. The authors suggest that the CBD-mediated attenuation of fearful responding was not likely due to an anxiolytic effect as there was no evidence of reduced anxiety following CBD administration. The authors also suggest that CBD may be a potential adjunct to extinction-based therapies for anxiety disorders and warrant further investigation.

A preliminary, open-label, pilot clinical study of add-on oral THC (25 mg/mL) in 10 patients with chronic PTSD and on stable medication (e.g. duloxetine, escitalopram, mirtazapine, buproprion, clonazepam, lorazepam) reported a statistically significant improvement in global symptom severity, sleep quality, frequency of nightmares and PTSD hyperarousal symptoms over the three-week study period [571]. Participants were instructed to begin dosing by placing 2.5 mg of THC b.i.d. (i.e. 0.1 mL of a 25 mg/mL olive oil solution containing THC) beneath the tongue, 1 h after waking up and 2 h before going to bed. Maximum daily dose was 5 mg THC b.i.d. (i.e. 0.2 mL b.i.d.), or a total 10 mg daily dose (i.e. 0.4 mL). A statistically significant decrease in symptom severity was observed in PTSD hyperarousal symptoms, clinical global impression scale (CGI-S), clinical global impression improvement (CGI-I), sleep quality, frequency of nightmares, and total Nightmare Effects Survey (NES) scores. Twenty percent of participants attained complete remission of nightmares by week 3. Adverse effects were reported in 40% of the subjects and consisted of dry mouth, headache, and dizziness. Limitations of this study included small sample size, open-label design and no placebo control as well as short follow-up period.

An open-label, non-placebo-controlled clinical trial of nabilone for PTSD was conducted in 47 non-military, civilian patients diagnosed with PTSD, 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 [578]. 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.

A preliminary, randomized, double-blind, placebo-controlled cross-over clinical study of 10 Canadian male military personnel with PTSD who were not responsive to conventional treatment and who continued to experience trauma-related nightmares, received 0.5 mg nabilone or placebo and titrated to the effective dose (i.e. nightmare suppression) or to a maximum daily dose of 3 mg nabilone [1038]. Average daily dose achieved for nabilone was 2.0 mg/day. Treatment arms lasted for seven weeks each, with a two-week washout period in between. Score on the Global Impression of Severity of PTSD was 3.3 at screening (4 = extreme). The mean reduction in nightmares measured by the Clinician-Administered PTSD Scale (CAPS) for Recurring and Distressing Dream scores were -3.6 and -1.0 in the nabilone and placebo groups respectively ($p = 0.03$). Mean global improvement measured by the Clinical Global Impression of Change scale was statistically significant between the nabilone and placebo groups. Half (50%) of the subjects reported a significant improvement in nightmare suppression on nabilone, while only 11% of subjects reported improvement with placebo. Mean scores for the General Well-Being Questionnaire showed a difference from baseline of 20.8 and -0.4 for the nabilone and placebo groups respectively. Incidence rates of adverse events in the nabilone and placebo groups were approximately the same (50% vs. 60%, respectively). The most common adverse effects associated with nabilone treatment were dry mouth and headache. There were no serious adverse events or subject dropout. While the study findings are promising, the sample size was very small.

A recent systematic review found "insufficient evidence" around the benefits and harms of cannabis in treating PTSD among adults. Only five studies met inclusion criteria (pharmaceutical cannabinoids were excluded), two of which were systematic reviews that came to similar inconclusive conclusions with the current review, and three of which were observational studies, with two showing no association between cannabis use and PTSD outcomes, and one showing that cannabis use was longitudinally associated with more severe levels of PTSD symptoms compared to cannabis abstainers. The authors emphasized that evidence was too limited to draw any conclusions and clinical trials and more cohort-based studies are needed to determine the safety and efficacy of plant-based cannabis for PTSD [1064].

4.9.5.4 Alcohol and opioid withdrawal symptoms (drug withdrawal symptoms/drug substitution)

- ***Pre-clinical studies suggest CB_1 receptor agonism (e.g. THC) may help increase the reinforcing properties of alcohol, increase alcohol consumption, and increase risk of relapse of alcohol use, as well as exacerbate alcohol withdrawal symptom severity.***
- ***Pre-clinical studies suggest certain cannabinoids (e.g. THC) may alleviate opioid withdrawal symptoms.***
- ***Evidence from observational studies suggests that cannabis use could help alleviate opioid withdrawal symptoms, but there is insufficient clinical evidence from which to draw any reliable conclusions.***

There is increasing interest in the use of cannabis as a substitute for alcohol, opioids and other drugs, including illicit drugs, both in terms of decreasing drug withdrawal symptoms associated with abstinence from such drugs, but also in the context of decreasing some of the health risks associated with use of these drugs (e.g. opioid-associated morbidity and mortality). In the case of opioids, *in vitro* and *in vivo* studies have shown significant physiological and pharmacological overlap, cross-tolerance, mutual potentiation, and cross-talk between the endocannabinoid and the endogenous opioid systems (see **Section 4.7.2.3**) [1065, 1066]. In addition, both of these endogenous physiological mechanisms have been implicated in the mechanism of action of several other drugs with abuse and dependence potential such as ethanol, nicotine, and psychostimulants [1065].

A survey that examined patterns of cannabis use and medical conditions and symptoms (**C**annabis **A**ccess for **M**edical **P**urposes **S**urvey, **CAMPS**) among 473 self-identified current users of cannabis for medical purposes reported that over 80% of respondents self-reported substituting cannabis for prescription drugs, over 51% for alcohol and over 32% for illicit substances [1067]. Median weekly amount of cannabis used was 14 g (or 2 g per day). The most commonly endorsed reasons for substitution were "less adverse side effects" and "better symptom management". Limitations of the study included self-report and lack of physician confirmation of medical conditions and extent of patient improvement (or lack thereof) as well as the potential for multiple responses from a single respondent and a biased sample population with an over-representation of individuals responding favorably to cannabis.

Alcohol

There is evidence to suggest complex functional interactions between ethanol and the ECS (reviewed in [1068]). Acute and chronic administration of ethanol in animals is associated with brain region-specific changes in endocannabinoid levels (*acute*: increases/decreases in endocannabinoid levels; *chronic*: increases in endocannabinoid levels) and in the expression of ECS components (*chronic*: decreases in levels of CB_1 receptor, and of FAAH) [212]. In human studies, acute administration of ethanol was associated with an increase in CB_1 receptor availability, whereas chronic consumption of ethanol (i.e. in alcoholic patients) was associated with a significant reduction in CB_1 receptor availability (20 – 30%) persisting at least two to four weeks into abstinence [1069, 1070]. Chronic alcohol consumption was also associated with decreased levels of FAAH, decreased CB_1 receptor coupling to G proteins and decreased FAAH activity [212]. CB_1 receptor agonism as well as genetic deletion of *FAAH,* or its pharmacological inhibition, appears to mediate the reinforcing properties of ethanol, facilitates ethanol consumption, and enhances re-instatement of ethanol self-administration in animal models [1068]. On the other hand, genetic ablation of CB_1 receptor expression or its pharmacological inhibition (e.g. by rimonabant) generally results in decreased ethanol consumption in animal models [212]. There is also some limited and mixed evidence gathered from animal studies that suggests the ECS may be involved in the modulation of alcohol withdrawal symptoms; with CB_1 receptor agonism (e.g. by THC and nabilone) apparently exacerbating withdrawal severity and conversely, CB_1 receptor antagonism either mitigating or worsening alcohol withdrawal symptoms [212, 1071-1074].

Opioids

Anecdotal information and findings from some animal studies suggest that cannabinoids (e.g. THC) might be useful in treating the symptoms associated with opioid withdrawal [843, 1075-1078], but there are no supporting clinical studies of efficacy in this regard. Nevertheless, 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 [842]. One literature review suggests that under certain circumstances, cannabis use can be associated with positive treatment prognosis among opioid-dependent cohorts [1066]. Cannabis abuse and dependence were predictive of decreased heroin and cocaine use during treatment, and intermittent use of cannabis was associated with a lower percentage of positive opioid urine drug screens and improved medication compliance on naltrexone therapy [1066]. A few qualitative studies have found that people who use heroin report that they are able to reduce their heroin use by using cannabis [1079, 1080]. In one study looking at people who inject drugs (PWID), smoking cannabis was reported to reduce anxiety and craving experienced while transitioning away from daily heroin use [1079], while in another study, medical cannabis patients reported using cannabis to substitute or wean off prescription opioids [1080]. Another study found that street-recruited PWIDs who reported using cannabis used opioids (i.e. heroin) less frequently [1081]. However, a study that investigated the use of smoked cannabis to alleviate symptoms of opioid withdrawal did not appear to find any effect of cannabis use on opioid-withdrawal symptoms [1082]. In this study, 116 outpatient heroin and cocaine users (of whom 46 were also cannabis users) participating in a 10-week methadone-taper phase of a randomized clinical trial were assessed for self-rated opioid withdrawal symptoms. The study found that opioid withdrawal scores did not differ between users and non-cannabis users suggesting that smoked cannabis did not reduce opioid withdrawal symptoms in this patient population. Lastly, in a five-week, placebo-controlled, randomized, double-blind, safety study of dronabinol for the treatment of moderate-intensity opioid withdrawal symptoms in opioid-dependent adults, doses of 5 or 10 mg of dronabinol were well-tolerated, while doses of 20, 30 or 40 mg dronabinol produced sustained elevations in heart rate and anxiety/panic in some subjects [1083].

4.9.5.5 Schizophrenia and psychosis

- ***Significant evidence from pre-clinical, clinical and epidemiological studies supports an association between cannabis (especially THC-predominant cannabis) and THC, and an increased risk of psychosis and schizophrenia.***
- ***Emerging evidence from pre-clinical, clinical and epidemiological studies suggests CBD may attenuate THC-induced psychosis.***

Schizophrenia is a chronic and devastating mental disorder which typically manifests in late adolescence or early adulthood [1084]. It is characterized by so-called positive symptoms, negative symptoms, and cognitive impairment [1085]. Positive symptoms include suspiciousness, paranoid and grandiose delusions, conceptual disorganization, fragmented thinking, and perceptual alterations [1085]. On the other hand, negative symptoms include blunted affect, emotional withdrawal, psychomotor retardation, lack of spontaneity and reduced rapport [1085]. Cognitive deficits include deficits in verbal learning, short-term memory, working memory, executive function, abstract ability, decision-making, and attention [1084, 1085]. By comparison, psychotic-like episodes are characterized by derealisation, depersonalization, dissociation, hallucination, paranoia, impairment in concentration, and perceptual alterations and are typically of a transient and self-limited nature [1085].

Below is a discussion of the role of the ECS in schizophrenia and psychosis as well as a discussion of the role of THC and CBD in these disorders. While the evidence strongly suggests exposure to THC is detrimental to individuals who have a personal or family history of schizophrenia, the available evidence also suggests a potential anti-psychotic/anti-schizophrenic role for CBD, though additional research is required.

The endocannabinoid system and psychotic disorders

There is increasing evidence implicating the ECS in schizophrenia and psychosis [177, 1085, 1086]. Findings from blood and CSF samples, and post-mortem, neuroimaging, and genetic studies lend strong support to the involvement of the ECS in schizophrenia and psychosis [177]. For example, levels of anandamide were reported to be significantly elevated in the CSF and serum of patients with initial prodromal states of psychosis [1087]. In addition, anandamide levels were also elevated in the CSF and serum of anti-psychotic-naïve patients with active schizophrenia [1088, 1089]. Treatment of schizophrenic patients with dopamine D2 receptor antagonists (standard pharmacologic treatment for schizophrenia) also lowers anandamide levels to normal [1090, 1091]. Post-mortem studies investigating CB_1 receptor densities in the brains of deceased schizophrenic patients have also noted an upregulation of CB_1 receptor levels in the dorsolateral pre-frontal cortex, anterior cingulate cortex, and posterior cingulate cortex [1092-1096], areas of the brain typically afflicted in schizophrenia [1086]. Neuroimaging studies measuring *in vivo* CB_1 receptor availability in schizophrenic patients also report a widespread increase in CB_1 receptor levels in a number of other brain areas including the nucleus accumbens, insula, cingulate cortex, inferior frontal cortex, parietal cortex, mediotemporal lobe, and the pons [1097, 1098]. Genetic studies suggest that polymorphisms in a number of different genes such as *catechol-O-methytransferase* (*COMT*), *AKT Serine/Threonine Kinase 1* (*AKT1*), *dopamine active transporter 1* (*DAT1*), *cannabinoid receptor 1* (*CNR1*), and *BDNF* may increase individual vulnerability to psychosis and schizophrenia (see below and also **Section 7.7.3.2**) especially when interacting with environmental factors such as urbanicity, abuse/maltreatment/trauma, and cannabis or other substance use [1085].

Comorbidity of substance use disorders with psychotic disorders

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 [1099, 1100]. 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. patients with schizophrenia) consume cannabis in order to alleviate specific psychopathological symptoms or alternatively to diminish the side effects resulting from the use of medications [1100, 1101]. For example, a recent review examining the reasons for cannabis use among individuals with psychotic disorders reported that the most common reasons for cannabis use in this population were related to the desire to improve mood and alleviate dysphoria, to relax and increase pleasure, to get "high", to decrease anxiety, to improve social life and to reduce boredom [1102]. However, the authors note that despite the beneficial reasons and positive subjective effects claimed by individuals with psychotic disorders using cannabis, evidence suggests a deterioration in the positive symptoms of some patients and worse treatment adherence and clinical course with cannabis use. Further evidence against the "self-medication" hypothesis also comes from research suggesting that cessation of cannabis use in patients with schizophrenia is associated with an improvement in overall and cognitive functioning, as well as psychotic and depressive symptoms [1103]. Indeed, a recent systematic review and meta-analysis showed that independent of stage of illness, continued cannabis use in patients with a pre-existing psychotic disorder was associated with a greater increase in relapse of psychosis compared to patients who never used or discontinued use [164]. Continued use was also associated with longer hospital admissions. Furthermore, there was a greater effect of continued use over discontinued use on relapse, positive symptoms, and level of functioning, but not on negative symptoms. A subsequent observational study of patients 18 – 65 years of age with first-episode psychosis showed that former regular users of cannabis who stopped after the onset of psychosis had the most favourable illness course with regards to relapse [165]. Continued high-frequency use (i.e. daily use) of high-potency (skunk-like) cannabis had the worst outcome (increased risk for subsequent relapse, more relapses, fewer months until relapse, and more intense psychiatric care). Another recent prospective cohort study reported that it is more likely than not that continued cannabis use after onset of psychosis is causally, and dose-dependently, associated with increased risk of relapse of psychosis resulting in psychiatric hospitalization [166]. While the "self-medication" hypothesis presents a compassionate, interesting, and attractive explanation to understand why schizophrenics have co-morbid substance abuse disorders, the evidence presented here as well as the lack of a relationship between early psychotic symptoms and an increased risk of later cannabis use have called the hypothesis into question [1104-1106]. On the other hand, the "addiction-vulnerability" hypothesis claims that substance abuse vulnerability and schizophrenic symptoms share a common neuropathology [1105, 1107]. 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

There is much scientific evidence to suggest a robust positive association between cannabis use, especially THC-predominant cannabis, and the development of acute and persistent psychosis in some individuals, earlier onset of schizophrenia (especially in adolescents susceptible to psychotic disorders, [187, 188, 196, 199, 202]), as well as exacerbation of existing symptoms and a more complicated course of treatment in those who already suffer from schizophrenia [539, 1085, 1102, 1105, 1108, 1109]. Despite these findings, the evidence suggests that cannabis is neither necessary nor sufficient to cause a persistent psychotic disorder; it appears instead that cannabis is but one factor that interacts with other factors to result in psychosis [183]. Increasing evidence suggests that the link between cannabis and psychosis is further moderated by age at onset of use, childhood abuse (stressors), and genetic vulnerability [183].

Adolescence and young adulthood are critical developmental periods, and exposure to a variety of environmental stimuli, including cannabis, can adversely affect the proper course of neurobiological development and trigger the early onset of schizophrenia in those with a genetic vulnerability [539, 1085, 1109-1111]. The period of brain maturation during adolescence spans from age 10 to 24 with continued synaptogenesis, myelogenesis, dendritic and synaptic pruning, volumetric growth, changes in receptor distribution, and programming of neurotrophic levels during this time, especially in the prefrontal cortex and the limbic system [540, 1106]. Adolescence is also the period of time where the brain's ECS undergoes dynamic changes including a spike in mRNA levels of the CB_1 receptor, a steady increase in the level of anandamide, and a more pronounced decrease in the levels of 2-AG [539]. The ECS is implicated in the myelination of various tracts and in neuroplasticity and synaptic function [539]. It is therefore conceivable that exogenously applied cannabinoids such as THC can perturb the fine balance of endocannabinoid levels and the proper functioning of the CB_1 receptor resulting in a change in course of neurodevelopment during this period. In one case-control study with 280 people with a first episode of psychosis and 174 controls, patients reported using higher-potency cannabis containing high THC and low CBD compared to the controls who reported using cannabis containing equal amounts of THC and CBD [1112]. Furthermore, daily use of high potency cannabis, containing high amounts of THC and low amounts of CBD, was associated with an earlier age of onset of psychosis [1113]. Individuals who started using cannabis at age 15 or younger also had an earlier onset of psychosis than those who started after age 15 [1113].

Studies of animal models of schizophrenia report that chronic treatment of adolescent rats, but not adult rats, with a cannabinoid receptor agonist results in a schizophrenia-like phenotype that is accompanied by changes in basal neuronal activity in various brain structures including the nucleus accumbens, amygdala, caudate putamen, and the hippocampus (see [1106, 1114, 1115]).

Meanwhile, 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 [201]. These symptoms included transient positive psychotic symptoms, perceptual alterations, negative symptoms, euphoria, anxiety, and cognitive deficits in attention, working memory, and verbal recall [201]. Likewise, intravenous administration of Δ^9-THC in *schizophrenics* was associated with transient exacerbation of core psychotic symptoms [199]. In summary, acute psychotomimetic symptoms associated with cannabis and/or THC-intoxication can include depersonalization, derealization, paranoia, ideas of reference, flight of ideas, pressured thought, disorganized thinking, persecutory delusions, grandiose delusions, auditory/visual hallucinations, and impairments in attention and memory (in about 20 – 50% of individuals) [1085]. These effects have been documented consistently with smoked cannabis, orally administered cannabis (5 – 20 mg THC) and intravenously administered THC (0.015 – 0.03 mg/kg) [1085].

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 *COMT* gene [1116-1123], and others have focused on polymorphisms at the *AKT1* gene [1124-1127]. 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. More recently, evidence has also emerged implicating polymorphisms at the *CNR1*, neuregulin 1 (*NRG1*) as well as the *DAT1* gene and the *BDNF* gene and THC/cannabis use with onset of psychotomimetic effects as well as earlier age of onset of schizophrenia [1085, 1128-1130]. Please consult **Section 7.7.3.2** 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 sections 7.7.3 and 7.7.3.2 suggest that cannabis use, especially THC-predominant cannabis, 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. In contrast, emerging evidence suggests CBD may protect against the psychosis-inducing effects of THC (see below).

Cannabidiol

In contrast to the harmful effects seen with THC and THC-predominant cannabis in psychosis and schizophrenia, there is some evidence from observational, and preliminary pre-clinical and clinical studies that suggests that CBD *may protect* against THC-induced psychosis and could even serve as a potential treatment for schizophrenia.

Observational studies

Two studies that analyzed cannabinoid levels in hair samples from 140 individuals found that those who had only THC in their hair exhibited greater positive symptoms with higher levels of hallucinations and delusions than those with both THC and CBD in their hair and those with no cannabinoids [1131, 1132]. On the other hand, another 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 between studies [535].

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 [139]. Furthermore, the study was hampered by a number of important methodological issues suggesting the conclusions should be interpreted with caution.

In one case-control study with 280 people with a first episode of psychosis and 174 controls, patients reported using higher-potency cannabis containing high THC and low CBD compared to the controls who reported using cannabis containing equal amounts of THC and CBD [1112]. Furthermore, daily use of high potency cannabis, containing high THC and low CBD, was associated with an earlier age of onset of psychosis compared to non-cannabis users [1113].

In a follow-up case-cohort study of 410 patients with first-episode psychosis and 370 population controls, daily use of “skunk-like” cannabis (very high THC, very low CBD), was associated with a more than five-fold increased risk of first-episode psychosis, whereas weekend use of “skunk-like” cannabis was associated with a nearly three-fold increased risk of first-episode psychosis [173]. By contrast, the OR of a first-episode psychosis associated with the use of “skunk-like” cannabis less than once per week, or daily, weekend, or less-than-weekly use of lower potency cannabis was not statistically significant compared with never use of cannabis [173].

The above evidence suggests that the presence of THC and the absence of CBD in cannabis may increase the risk of experiencing psychotic reactions and also suggests a dose-response effect between THC and risk of first episode psychosis.

Pre-clinical and clinical studies

Consistent with these findings, a number of pre-clinical and clinical studies have suggested that CBD may in fact protect against the psychoactive and psychosis-inducing effects of THC and THC-predominant cannabis, and may also have therapeutic use in the treatment of individuals with psychosis and schizophrenia [133, 135, 1133-1142]. One caveat to this is that in animal models it appears that pre-treatment with CBD 15 to 60 min prior to administration of THC, but not co-administration, is associated with increased blood and intracerebral levels of THC and THC-associated immobility [123, 131]. Furthermore, a higher ratio of CBD to THC also appears important in attenuating the psychoactive effects of THC [135, 1108, 1135].

Pre-clinical studies

Studies in certain rat and mouse models of psychosis suggest that CBD (at doses of 15 – 60 mg/kg or roughly equivalent human doses of 1.25 mg/kg to 10 mg/kg CBD) reduces psychotic-like behavioural effects in a manner comparable to that observed with atypical anti-psychotic drugs [1143, 1144].

Clinical studies with healthy volunteers

In perhaps one of the first clinical studies examining the effects of CBD on THC-induced psychoactivity, Karniol et al. administered placebo, THC (30 mg), CBD (15, 30 or 60 mg) or a combination of THC and CBD orally to 40 healthy male volunteers in a double-blind fashion and measured resulting subjective psychoactive effects [135]. Administration of 30 mg of THC resulted in strong psychological reactions (mainly anxiety), that in some cases reached a near-panic state, and significantly impaired performance on a time estimation task. Both of these effects were attenuated in a dose-dependent manner in the presence of increasing doses of CBD. A 2 : 1 ratio of CBD to THC (60 mg : 30 mg) was most effective in attenuating the intensity of the psychoactive effects induced by THC in this study. CBD appeared to modify not only the intensity but also the quality of the psychoactive effects induced by THC.

In another study of 15 healthy volunteers, simultaneous inhalation of CBD (150 µg/kg) and THC (25µg/kg) attenuated the subjective euphoria associated with THC and showed a trend towards a decrease in THC-induced psychomotor impairment [1134]. No effect on THC-induced euphoria and psychomotor impairment was noted when the same dose of CBD was administered 30 minutes before THC.

In a double-blind, placebo-controlled clinical study, eight healthy volunteers were orally administered placebo, THC (0.5 mg/kg), CBD (1 mg/kg), or a mixture of THC (0.5 mg/kg) and CBD (1 mg/kg) [133]. Administration of THC alone was associated with a number of psychoactive effects, including depersonalization, disconnected thoughts, paranoid ideas and anxiety that were mostly blocked when CBD was co-administered with THC.

In another clinical study of nine healthy volunteers, a 200 mg oral dose of CBD was able to attenuate the impairment in binocular depth inversion (a model of impaired perception during psychotic states) induced by 1 mg of oral nabilone [1141].

On the other hand, oral administration of a cannabis extract (containing 10 mg THC and 5.4 mg CBD), but not pure THC (10 mg THC), to 24 healthy volunteers in a placebo-controlled, double-blind clinical study was associated with decreased finger tapping frequency, a measure of motor disturbance related to schizophrenic symptomatology and severity of illness [1135].

A pseudo-randomized, placebo-controlled, double-blind, within-subject clinical study showed that pre-treatment of healthy human subjects with CBD (5 mg i.v.), but not placebo, diminished the emergence of positive psychotic symptoms 30 min after i.v. administration of 1.25 mg of Δ^9-THC [125].

In a randomized, double-blind, placebo-controlled clinical study of 48 healthy subjects that were administered placebo, THC (i.v. 1.5 mg) or CBD (p.o. 600 mg), CBD pre-treatment 3.5 h before THC administration attenuated THC-associated paranoia and impairment of episodic memory, but not working memory [1136].

Taken together, the above findings suggest CBD, especially at ratios of 2 : 1 and when co-administered, can attenuate the acute psychotic and anxiogenic effects as well as certain aspects of cognitive impairment observed with administration of THC.

Clinical and case studies in patients with psychotic symptoms

One case report of a 19-year-old female schizophrenic patient treated with haloperidol and oral CBD reported that treatment with 1500 mg CBD daily for 26 days, but not with haloperidol, was associated with an attenuation of psychotic symptoms [1137]. Another slightly larger case study by the same group reported a mild level of improvement in psychotic symptoms in one out of three treatment-resistant schizophrenic patients treated with 1280 mg oral CBD daily for four weeks; no adverse effects were noted [1139]. In a clinical study, again by the same group, six patients with PD who also experienced psychotic symptoms were treated with 600 mg/day oral CBD for four weeks [1145]. This treatment regimen was associated with a significant reduction in psychotic symptomatology without any adverse effects.

In a placebo-controlled, single-dose clinical study by Hallak et al. (2010), 28 schizophrenic patients were administered either placebo, 300 mg, or 600 mg CBD orally. While no improvements in psychotic symptomatology were noted, there were statistically significant improvements in attention with the placebo and the 300 mg CBD dose, but not the 600 mg dose of CBD where there appeared to be a potential worsening of attention possibly due to a sedative effect at the higher dose [1140].

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 [1142]. 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 increased prolactin release). In addition, CBD did not appear to significantly affect either hepatic or cardiac functions. CBD treatment, but not amilsupride, was also associated with an increase in serum levels of anandamide.

Taken together, the available evidence from a limited number of emerging observational, pre-clinical and clinical studies suggests that CBD may play a protective role against the manifestation of transient psychotic symptoms associated with exposure to THC or THC-predominant cannabis. CBD may also hold therapeutic promise in the treatment of individuals with psychotic symptoms or schizophrenia, though additional research is needed in this regard to confirm and substantiate this effect.

That being said, 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, whether for non-medical or medical purposes, typically contains relatively low levels of CBD and higher levels of THC [76, 1146]. For example, the CBD content of street cannabis typically varies between 0.1 and 0.5%, although CBD levels of up to 8.8% (in hashish) have been noted [139]. Therefore, as an example, 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) [1147]. Some strains of dried cannabis sold for medical purposes by Canadian producers licensed by Health Canada can contain as much as 24% CBD with little THC. Therefore, a 1 g joint of this strain of cannabis could contain up to 240 mg of CBD; still far lower a dose than that used in clinical trials of CBD for psychosis/schizophrenia. However, many licensed producers also sell cannabis strains with approximately equal concentrations of THC and CBD, and some with a 2 : 1 CBD to THC ratio which has been reported as potentially helping to reduce the incidence of psychotic symptoms in individuals using cannabis. Though additional research is needed, patients who reported using cannabis with approximately equal levels of THC and CBD reported less perturbation of mood [118]. Furthermore, licensed producers of cannabis for medical purposes are now also permitted to produce and sell cannabis oil, which can contain high levels of CBD (i.e. up to 24%).

In conclusion, consumption of cannabis that contains mainly THC as well as consumption of other psychoactive cannabinoids (e.g. dronabinol, nabilone) should be treated with considerable caution in

patients with schizophrenia (or those at risk for psychosis) 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 in the treatment of schizophrenia/psychosis, while promising, requires further research.

4.9.6 Alzheimer's disease and dementia

- ***Pre-clinical studies suggest that THC and CBD may protect against excitotoxicity, oxidative stress and inflammation in animal models of Alzheimer's disease (AD).***
- ***Limited case, clinical and observational studies suggest that oral THC and nabilone are associated with improvement in a number of symptoms associated with AD (e.g. nocturnal motor activity, disturbed behaviour, sleep, agitation, resistiveness).***

Dementia affects 36 million people worldwide where Alzheimer's disease (AD) accounts for 60 to 80% of these cases [557]. While still a subject of some debate, a widely accepted theory underlying the pathophysiology of AD is that the deposition of amyloid-beta (Aβ) protein in specific brain regions leads 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 [1148]. These pathological processes are thought to give rise to disease-associated symptoms such as memory deficits, and cognitive and motor impairments [1148].

The endocannabinoid system and Alzheimer's disease

There is some evidence to suggest an association between the ECS and the pathophysiology of AD [1148, 1149]. One *in vivo* study reported elevation in the levels of the endocannabinoid 2-AG in response to intra-cerebral administration of $A\beta_{1-42}$ peptide in animals [1150]. Another study using *post-mortem* brain samples from deceased AD patients showed that decreased anandamide levels were associated with increasing $A\beta_{1-42}$ levels, but not with $A\beta_{40}$ levels, amyloid plaque load, or tau protein phosphorylation [1151]. Lastly, upregulation of CB_2 receptors and FAAH (and FAAH activity) has been respectively observed in reactive microglia and astrocytes surrounding senile plaques in *post-mortem* brain tissues collected from AD patients [1152].

Pre-clinical data

Pre-clinical studies suggest the ECS protects against excitotoxicity, oxidative stress, and inflammation — all key pathological events associated with the development of AD [1153].

Results from *in silico* and *in vitro* experiments suggest Δ^9-THC could bind to and competitively inhibit acetylcholinesterase, which in the context of AD functions as a molecular chaperone and accelerates the formation of amyloid fibrils and forms stable complexes with Aβ [1154]. In this way, Δ^9-THC blocked the amyloidogenic effect of acetylcholinesterase, diminishing Aβ aggregation [1154]. Other *in vitro* studies suggest that CBD may have neuroprotective, anti-oxidant, and anti-apoptotic effects, as well as the ability to prevent tau protein hyperphosphorylation in cellular models of AD [1155-1157]. It has also been shown that endocannabinoids can prevent Aβ-induced lysosomal permeabilization and subsequent neuronal apoptosis *in vitro* [1153]. An *in vivo* study reported that enhancement of endocannabinoid tone through inhibition of FAAH was associated with significant decreases in the amount of total amyloid precursor protein (APP), soluble $A\beta_{1-40}$, and $A\beta_{1-42}$ peptides and neuritic plaque density as well as decreased microgliosis and astrogliosis in a mouse model of AD [1158].

In vivo studies resported that CBD 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 [1159]. 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 [1160].

Administration of non-psychoactive doses of THC-enriched botanical extract (67.1% THC, 0.3% CBD, 0.9% CBG, 0.9% CBC, and 1.9% other phytocannabinoids), a CBD-enriched botanical extract (64.8% CBD, 2.3% THC, 1.1% CBG, 3.0% CBC, and 1.5% other phytocannabinoids) or nabiximols (combination of THC and CBD, 2.7% THC and 2.5% CBD) for a period of five weeks at the early stages of the symptomatic phase blunted the memory impairment observed in AβPP/PS1 mice [1161]. Furthermore, chronic exposure to THC-enriched botanical extract, but not CBD-enriched extract or nabiximols, resulted in reduced memory performance in wild-type mice compared to vehicle-treated littermates. While chronic treatment with THC, CBD or nabiximols did not significantly modify the total Aβ burden in the cortex or hippocampus of AβPP/PS1 mice, the combination of THC and CBD (nabiximols) reduced soluble $A\beta_{1-42}$, but not $A\beta_{1-40}$, protein levels suggesting a protective effect. THC, CBD or combination of both (nabiximols) was also associated with a reduction in astrogliosis associated with Aβ deposition and the combination of THC and CBD also significantly reduced microgliosis.

Clinical and observational data

There have been very few clinical studies of cannabis or cannabinoids for the treatment of AD. A 2009 Cochrane database systematic review of cannabinoids for the treatment of dementia concluded that there was insufficient clinical evidence to suggest that cannabinoids can be effective at improving disturbed behavior in dementia or in the treatment of other symptoms of dementia [1162]. For the moment, no firm conclusions can be drawn about the safety and efficacy of cannabinoid-based drugs in older individuals, which represent the population most likely to be affected by AD [557].

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 and an increase in body weight [1163]. However, adverse reactions such as fatigue, somnolence, and euphoria (presumably unwanted) were reported. 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 [1164]. A placebo-controlled clinical study of 24 patients diagnosed with probable dementia of the Alzheimer-type with agitated behavior and given dronabinol (2.5 mg, b.i.d., for two weeks) showed reduced nocturnal motor activity compared to baseline with no reported incidence of adverse events [1165]. 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) which provided immediate reduction in the severity of agitation and resistiveness and eventual improvement in various behavioural symptoms following six weeks of continuous treatment [1166]. A case-report of a 71-year old man with mixed vascular and frontotemporal dementia accompanied by sexual disinhibition reported failure to curb his behaviours despite trials with a variety of agents including sertraline, divalproex, trazodone, risperidone, and aripiprazole [1167]. Treatment with nabilone (0.5 mg every 8 h) resulted in significant improvement in behavioural symptoms, however sedation and lethargy were noted but *only* during the dose titration phase.

A retrospective chart review evaluated the data of 40 patients with dementia (13 with AD) who had been treated with dronabinol for an average of 17 days (range: 4 – 50 days) for behavioural or appetite disturbances [421, 557, 1168]. Administration of an average dronabinol dose of 7 mg/day was associated with significant improved scores on the Pittsburgh Agitation Scale and the Clinical Global Impression Scale, but not on the Global Assessment of Functioning Scale [421, 557, 1168]. Significant improvements were noted in sleep duration and percentage of food consumed during dronabinol treatment. Twenty-six adverse events were detected in the study and the most frequent events included sedation, delirium, urinary tract infection, and confusion [1168]. While causality was not established, the adverse events did not lead to medication discontinuation.

It is unclear if the improvement in symptoms of AD associated with the use of psychoactive cannabinoids (THC, nabilone) are related to their non-specific sedative effects or to cannabinoid-specific mechanisms of action as some studies report sedation, somnolence, and fatigue while other reports suggests these adverse effects are transient and wear-off once the patient has passed the initial dose titration phase and has reached a stable dose of cannabinoid.

Nevertheless, 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 MS [233]. Similar adverse effects of cannabis/cannabinoids on cognition could potentially apply in the context of Alzheimer-type dementia.

4.9.7 Inflammation

The role of the ECS in inflammation is complex as this system has been implicated in both pro- and anti-inflammatory processes [1149]. Endocannabinoids, such as anandamide and 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 [1169]. 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 [1169, 1170]. For information on other diseases with an inflammatory component such as the arthritides or IBD, please consult **Sections 4.8** and **4.9.8.2**, respectively, of this document.

4.9.7.1 Inflammatory skin diseases (dermatitis, psoriasis, pruritus)

- ***The results from pre-clinical, clinical and case studies on the role of certain cannabinoids in the modulation of inflammatory skin diseases are mixed.***
- ***Some clinical and prospective case series studies suggest a protective role for certain cannabinoids (THC, CBD, HU-210), while others suggest a harmful role (cannabis, THC, CBN).***

The skin possesses an ECS [43]. CB_1 and CB_2 receptors are expressed in a number of skin cell types including epidermal keratinocytes, cutaneous nerves and nerve fibres, sebaceous cells, myoepithelial cells of eccrine sweat glands, sweat gland ducts, mast cells, and macrophages [1171]. The ECS 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 [43, 1172-1174].

Pre-clinical and clinical studies

A pre-clinical study in mice with dinitrophenol fluorobenzene (DNFB)-induced allergic contact dermatitis reported that a topical solution containing 1 µM THC applied to the skin was associated with an attenuation of the inflammatory response that was independent of CB_1/CB_2 receptors [1175]. Another pre-clinical study reported that application of CBD (10 µM) to cultured human sebocytes and to a human skin organ culture inhibited the lipogenic ("pro-acne") actions of various compounds and suppressed sebocyte lipogenesis and proliferation while also exerting anti-inflammatory effects, raising the possibility that CBD may have the potential to act as an "anti-acne" therapy [1176]. Another *in vitro* study showed that CBD and CBG (0.5 µM), but not CBDV, significantly reduced the expression of a number of genes expressed in differentiated human keratinocytes (i.e. keratins, involucrin, and transglutaminase) by increasing DNA methylation of the keratin 10 gene [1177]. CBD also increased global DNA methylation levels raising the possibility that CBD can exert epigenetic control of skin differentiation and potentially pave the way towards new phytocannabinoid-based approaches to treating skin diseases, according to the authors of the study.

In clinical studies, experimentally-induced histamine-triggered pruritus was reduced by peripheral administration of the potent synthetic CB_1/CB_2 receptor agonist HU-210, and the accompanying increases in skin blood flow and neurogenic mediated flare responses were attenuated [1178]. In another clinical 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 [1179]. More recently, three prospective case series reported on the use of a topical preparation of cannabis (prepared in sunflower oil) for pyoderma gangrenosum [1180]. Between 0.5 and 1.0 mL of two different formulations of topical cannabis oils were used in the treatments (5 mg/mL THC and 6 mg/mL CBD; and 7 mg/mL THC and 9 mg/mL CBD), applied to the wound daily and up to 3 times daily, with additional application two to three times daily for breakthrough pain. Application of the topical cannabis oil preparation was associated with onset of analgesia within 5 minutes, with all cases demonstrating clinically significant reduction of pain greater than 30% and an accompanying statistically significant opioid-sparing effect.

A recent review of topical cannabinoids for inflammatory disorders and pain management concluded that despite promising data in rodent models, there are no rigorous studies confirming either safety or efficacy in humans [1181]. With interventions that lead to active areas of wound healing, the application of topical cannabinoid products may increase the risk for contamination and infection unless the product is rigorously tested and approved for dermatological use.

There have also been some case-reports of contact urticaria following exposure to cannabis flowers, and extreme sensitization to Δ^9-THC and CBN has also been observed in an animal model of contact dermatitis [1182, 1183] (and see **Section 7.3** for additional information on hypersensitivity/allergy to cannabis).

Therefore, while it is possible that some cannabinoids (e.g. HU-210, CBD) may have therapeutic value in the treatment of certain inflammatory skin conditions (such as psoriasis, pruritus, dermatitis, and acne), it is also possible for some cannabinoids (cannabis, THC, CBD) to trigger adverse skin reactions. Much further research is required in this area.

4.9.8 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 GI disorders (e.g. diarrhea, inflammation, and pain of GI origin) [1184-1186].

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 of the GI tract (enteric 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 [30, 31]. CB_2 receptor expression appears to be upregulated in sections of the colon in patients with IBD [33]. While the expression and localization of endocannabinoid synthesizing enzymes have not been well determined [33], studies in animals indicate that the endocannabinoid degradative enzymes FAAH and MAGL can be found in the enteric nervous system and other sites in the GI tract [33]. 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 [33]. 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 [1187]. There also appears to be some regional variation in the levels of endocannabinoids in the gut; 2-AG appears to be more abundant in the ileum than the colon, whereas the opposite is true of anandamide [33]. CB_1 and CB_2 receptors appear to be expressed in the pancreas [32], whereas the CB_1, but not the CB_2 receptor, is expressed in the liver under normal conditions [34, 35].

Cannabinoids appear to have many functions in the digestive system including the inhibition of gastric acid production, GI motility, secretion and ion transport, and the attenuation of visceral sensation and inflammation (reviewed in [33]). Perturbations in the levels of various components of the ECS have been noted in experimental animal models of GI disorders, as well as in clinical studies (reviewed in [33]). The sections below summarize the information regarding the uses of cannabis and cannabinoids in the treatment of various disorders of the GI system.

4.9.8.1 Irritable bowel syndrome

- ***Pre-clinical studies in animal models of irritable bowel syndrome (IBS) suggest that certain synthetic cannabinoid receptor agonists inhibit colorectal distension-induced pain responses and slow GI transit.***
- ***Experimental clinical studies with healthy volunteers reported dose- and sex-dependent effects on various measures of GI motility.***
- ***Limited evidence from one small clinical study with dronabinol for symptoms of IBS suggests dronabinol may increase colonic compliance and decrease colonic motility index in female patients with diarrhea-predominant IBS (IBS-D) or with alternating pattern (alternating constipation/diarrhea) IBS (IBS-A), while another small clinical study with dronabinol suggests a lack of effect on gastric, small bowel or colonic transit.***

Irritable bowel syndrome (IBS) is the most common functional GI disorder encountered in clinical medicine [1188]. It is a spectrum of disorders characterized by the presence of chronic abdominal pain and/or discomfort and alterations in bowel habits [1188, 1189]. Symptom patterns can be divided into diarrhea predominant (IBS-D), constipation predominant (IBS-C), and an alternating pattern (alternating constipation/diarrhea) (IBS-A) [1189, 1190]. 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 [1188]. There is also some emerging evidence that suggests an association between genetic alterations in genes coding for certain ECS proteins (e.g. *FAAH* and *CNR1*) and the pathophysiology of IBS [1191-1193].

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 intraperitoneal injection of different synthetic cannabinoid receptor agonists inhibited pain-related responses to experimentally-induced colorectal distension when administered *prior* to the experimental stimulus [1194]. 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 [1195]. 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 [1196].

Clinical data with dronabinol

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

One double-blind, randomized, placebo-controlled, parallel-group clinical study examined the effects of dronabinol on GI transit, gastric volume, satiation, and post-prandial symptoms in a group of healthy volunteers [1197]. A 5 mg dose of dronabinol was associated with a significant delay in gastric emptying in female subjects, but not male subjects. No significant differences in either small bowel or colonic transit were observed between subjects administered dronabinol or placebo in any gender group. 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. Adverse effects associated with the consumption of a 5 mg dose of dronabinol included dizziness/light-headedness, dry mouth, disturbed mental concentration, and nausea.

A subsequent double-blind, randomized, placebo-controlled, parallel-group clinical study investigated the effects of dronabinol on colonic sensory and motor functions of healthy human volunteers [1198]. 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. 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 [1198-1200]. Decreased compliance is typically associated with urgency and diarrhea, while increased compliance is typically associated with constipation [1199, 1201]. 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 [1198].

A double-blind, randomized, parallel-group clinical 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)) [1202]. Only the highest dose of dronabinol tested (5 mg) was associated with a small, but statistically significant, increase in colonic compliance. 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. 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. Sensation thresholds and sensation scores for gas and pain during experimentally-induced ramp distensions did not differ significantly among the different treatment groups. 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.

A subsequent double-blind, randomized, placebo-controlled, parallel-group clinical 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 [1203]. 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. 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.

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

- ***Pre-clinical studies in animal models of inflammatory bowel disease (IBD) suggest that certain cannabinoids (synthetic CB_1 and CB_2 receptor agonists, THC, CBD, CBG, CBC, whole plant cannabis extract) may limit intestinal inflammation and disease severity to varying degrees.***
- ***Evidence from observational studies suggests that patients use cannabis to alleviate symptoms of IBD.***
- ***A very limited number of small clinical studies with patients having IBD and having failed conventional treatments reported improvement in a number of IBD-associated symptoms with smoked cannabis.***

IBDs include Crohn's disease and ulcerative colitis [1204]. Crohn's disease is characterized by patchy trans-mural inflammation, which may affect any part of the GI tract [1205]. Symptoms include abdominal pain, diarrhea and weight loss as well as systemic symptoms of malaise, anorexia, and/or fever [1205]. Crohn's disease may cause intestinal obstruction due to strictures, fistulae, or abscesses [1205]. Ulcerative colitis is characterized by diffuse mucosal inflammation limited to the colon [1205]. Symptoms commonly include bloody diarrhea, colicky abdominal pain, urgency, or tenesmus [1205]. Both diseases are associated with an equivalent increased risk of colonic carcinoma [1205].

The endocannabinoid system and inflammatory bowel diseases
ECS changes have been observed in the GI tracts of experimental animal models of IBD, as well as in those of IBD patients [33, 1204]. These changes include changes in the levels of endocannabinoids, cannabinoid receptors, and endocannabinoid synthesizing and degrading enzymes [30, 33, 1204, 1206-1208].

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_1 and CB_2 receptors [1209-1214].

Acute colitis
Mice bearing a genetic deletion of the CB_1 receptor had a stronger colonic inflammatory response [1209] following rectal administration of dinitrobenzene sulfonic acid (DNBS), an established method of inducing an acute colitis-like phenotype in mice [1215]. In contrast to wild-type mice, histological examination of the colons of CB_1 receptor knockout mice treated with DNBS 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 [1209]. 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 [1209]. Furthermore, in contrast to CB_1 receptor knockout mice, wild-type mice retained a significantly greater body weight following DNBS treatment [1209]. Treatment of wild-type mice with the potent synthetic CB_1 and CB_2 receptor agonist HU-210, prior to and after DNBS insult, significantly reduced the macroscopic colonic inflammatory response [1209]. Mice bearing a genetic deletion of the FAAH enzyme also displayed an attenuated inflammatory response to DNBS compared to wild-type littermates [1209].

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 (TNBS)-induced acute colitis [1213]. 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. Genetic deletion of either or both CB receptors in mice treated with TNBS was also associated with significantly increased mRNA levels of various pro-inflammatory cytokines compared to TNBS-treated wild-type mice.

TNBS-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 [1216]. Intraperitoneal administration of CB_2 receptor agonists, prior to and following TNBS-induced colitis, was associated with a reduction in the macroscopic damage score which 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. Conversely, administration of a CB_2 receptor antagonist aggravated TNBS-induced colitis.

In a different experimental mouse model of acute colitis, the CB_1 receptor-selective agonist arachidonyl-2-chloroethylamide and the synthetic CB_2 receptor-selective agonist JWH-133, when injected intraperitoneally prior to and after colonic insult, significantly reduced colon weight gain, colon shrinkage, colon inflammatory damage score, and diarrhea [1212].

Inhibition of the 2-AG degrading enzyme MAGL in mice by intraperitoneal administration of a MAGL inhibitor *prior* to induction of acute colitis by TNBS was associated with decreased macroscopic and histological colon alterations, as well as decreased colonic expression of pro-inflammatory cytokines [1217]. Inhibition of MAGL was also associated with a reduction in colitis-related systemic and central inflammation in the liver and the CNS. 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.

Acute colitis and cannabidiol

Intraperitoneal injection of CBD (5 – 10 mg/kg) *prior* to DNBS-induced acute colitis was associated with a statistically significant attenuation of body weight loss caused by DNBS [1218]. CBD also reduced the wet weight/colon length ratio of inflamed colonic tissue, a marker of the severity and extent of the inflammatory response. Furthermore, CBD (5 – 10 mg/kg) significantly reduced macroscopic damage associated with DNBS 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). 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.

Another study reported that intraperitoneal (10 mg/kg) or intra-rectal (20 mg/kg) pre-treatment with CBD, again administered prior to induction of colitis by TNBS, caused a significant improvement of the colitis score and a decrease in the myeloperoxidase activity (a measure of neutrophil accumulation in colonic tissue) [1219]. 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. In contrast to the earlier study [1218], no differences in body weight were observed between vehicle-treated and CBD-treated mice that had developed colitis [1219].

The effects of intraperitoneal injections of THC, CBD, and a combination of THC and CBD on TNBS-induced acute colitis in rats have been investigated [1214]. 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. Myeloperoxidase activity, a measure of granulocyte infiltration, 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. 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 TNBS-induced colitis.

A more recent study investigated the effects of a whole-plant cannabis extract with high CBD content on an experimental model of intestinal inflammation [1220]. In this study, the authors showed that this extract, when given either intraperitoneally (at a dose of 30 mg/kg CBD) or by oral gavage (at a dose of 60 mg/kg CBD) following the manifestation of intestinal inflammation, decreased the extent of damage in the DNBS model of colitis. Furthermore, the extract, when administered at a starting dose of 1 mg/kg CBD (i.p.) and at 5 mg/kg (orally), dose-dependently reduced intestinal hypermotility in the croton oil model of intestinal hypermotility. However, while administration of pure CBD, at all doses tested, did not improve colitis, it did normalize croton oil-induced hypermotility both when given intraperitoneally and orally (at a dose of 5 mg/kg).

Acute colitis, cannabigerol and cannabichromene

A study that examined the effects of the non-psychotropic cannabinoid CBG on experimental IBD (i.e. colitis) reported that CBG at doses of 1 mg/kg i.p. (preventive) and 5 mg/kg i.p. (curative) administered either before (preventive) or after (curative) DNBS-induced acute colitis in mice significantly reduced the damaging effects of DNBS on colon weight/colon length ratio [1221]. In follow-up studies, a 30 mg/kg curative dose of CBG was associated with reductions in the signs of colon injury, submucosal oedema, cell proliferation, intestinal permeability, myeloperoxidase activity (i.e. intestinal inflammation), superoxide dismutase activity, inducible nitric oxide synthase (iNOS) and COX-2 expression, reactive oxygen species production, and IL-1β, IL-10, interferon- γ (IFN-γ) levels observed in DNBS-treated inflamed colons.

Another study that examined the effects of another non-psychotropic cannabinoid, CBC, on experimental IBD (i.e. colitis) in mice reported that administration of CBC (1 mg/kg, i.p.) was associated with a significant reduction in the damaging effects of DNBS on colon weight/colon length ratio, as well as a significant reduction in intestinal permeability, myeloperoxidase activity, intestinal erosion, and cell proliferation [1222]. *In vitro* studies further confirmed the anti-inflammatory effects of CBC [1222].

Chronic colitis
Intraperitoneal 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 [1223]. 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 [1223].

Ileitis
Ileitis is characterized by disruption of the mucosa, infiltration of lymphocytes into the sub-mucosa, increased myeloperoxidase activity, and vascular permeability [1224]. The effect of CBC on inflammation-induced hypermotility in a mouse model of intestinal ileitis has been studied [1224]. Administration of CBC (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 [1224]. CBC did not affect upper GI 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. [1224]. CBC also dose-dependently and significantly inhibited contractions induced by acetylcholine, as well as by electrical field stimulation, *in vitro* in ilea isolated from control mice and croton oil-treated mice [1224]. The inhibitory effect of CBC appeared to be cannabinoid receptor-independent [1224].

Information from surveys
It has been estimated that between 10 and 12% of patients with IBD are active cannabis users, and surveys conducted in patients with IBD report that between 44 and 51% of patients with IBD have used cannabis at some point in their lifetime [185, 372, 1225-1227]. Furthermore, between 10 and 50% of IBD patients use cannabis for disease symptom control (i.e. for symptoms such as abdominal pain, nausea and diarrhea) [185, 372, 1226, 1227].

Findings from a cross-sectional survey of 291 patients with IBD (Crohn's disease or ulcerative colitis) suggested that the vast majority of those patients reported using cannabis to relieve abdominal pain and to improve appetite [185]. In contrast to patients with Crohn's disease, a greater proportion of patients with ulcerative colitis reported using cannabis to improve diarrheal symptoms. In general, patients reported being more likely to use cannabis for symptom relief if they had a history of abdominal surgery, chronic analgesic use, alternative/complementary medicine use, and a lower SIBDQ (short IBD questionnaire) score. Both ulcerative colitis and Crohn's disease patients reported using cannabis to improve stress levels and sleep. The mean duration of cannabis use (current or previous) was seven years. The majority of cannabis users reported using once per month or less, but 16% reported using cannabis daily or several times per day. The vast majority (77%) of users reported smoking cannabis as a joint without tobacco, 18% of users smoked it with tobacco, 3% used a water pipe, and 1% reported oral ingestion. Approximately one-third of patients in this study reported significant side effects associated with the use of cannabis such as paranoia, anxiety, and palpitations. Other commonly reported side effects included feeling "high", dry mouth, drowsiness, memory loss, hallucinations, and depression.

A retrospective, observational study of 30 patients with Crohn's disease examined disease activity, use of medication, need for surgery, and hospitalization before and after cannabis use [372]. The average duration of disease was 11 years (range: 1 – 41 years). Twenty patients suffered from inflammation of the terminal ileum, five had inflammation of the proximal ileum, and eight had Crohn's disease of the colon. The indication for cannabis was lack of response to conventional treatment in the majority of the patients, and chronic intractable pain in most of the other patients. Most patients smoked cannabis as joints (0.5 g cannabis/joint), a few inhaled the smoke through water, and one patient consumed cannabis orally. Of those who smoked cannabis, most smoked between one and three joints per day. One patient smoked seven joints per day. The average duration of cannabis use was two years (range: two months to nine years). All patients reported that consuming cannabis had a positive effect on their disease activity. The scores on the Harvey-Bradshaw index (an index of Crohn's disease activity) were significantly decreased following cannabis use, and the use of other medications (e.g. 5-ASA, corticosteroids, thiopurine, methotrexate, and TNF antagonist) also appeared to be significantly reduced following use of cannabis. The study was limited by design and small size.

A population-based analysis of cases from the **N**ational **H**ealth **A**nd **N**utrition **E**xamination **S**urvey (**NHANES**) (2009-2010) of patients with ulcerative colitis or Crohn's disease vs. controls showed that subjects with IBD had a higher incidence of ever having used marijuana/hashish (i.e. 67% vs, 60%) as well as an earlier age of onset of the disease (i.e. 15.7 vs. 19.6 years) [1227]. Furthermore, IBD patients were less likely to have used marijuana or hashish daily, but they appeared to use more heavily when they did use (i.e. 65% with IBD used three or more joints per day vs. 81% without IBD that used two or fewer joints per day). Male sex and age over 40 appeared to predict marijuana/hashish use.

A prospective cohort survey study of 292 IBD patients examining the use of cannabis in IBD found that patients who reported using it for relief of symptoms associated with IBD (16%) reported using it to treat abdominal pain (90%), nausea and poor appetite (73% each), and diarrhea (42%) [1226]. The majority (61%) of cannabis-using patients in this survey reported smoking cannabis. Most cannabis-using patients also reported cannabis as being "very helpful" or "completely relieving" in treating the symptoms patients sought to relieve. Among past-users, the majority reported having used cannabis non-medically. Current cannabis users were younger than non-users, had lower SIBDQ scores, and were more likely to have chronic abdominal pain. Younger age, previous surgery, Crohn's disease and chronic abdominal pain predicted cannabis use for medical purposes. Current cannabis users were also more likely to be using narcotics to treat their abdominal pain than former users. Study limitations included possible patient recall bias, lack of objective measures of disease activity before and after cannabis use, and uncertainty around transposition of study findings to the broader IBD patient population.

A survey of 313 Canadian patients with IBD who reported using or not using cannabis for medical purposes examined the motives, patterns of use and subjective beneficial and adverse effects of patients who self-administered cannabis for medical purposes [1228]. The findings suggested that 18% of patients surveyed reported using cannabis to treat symptoms associated with IBD. The majority of these reported using cannabis to reduce symptoms rather than for prophylactic use. The majority of cannabis-using patients reported smoking cannabis (95%), while only 9% reported oral ingestion and 5% by drinking. Among the cannabis-using patients, 91% said they felt cannabis helped with their IBD and these patients reported that cannabis helped with abdominal pain (84%), improvement of abdominal cramping (77%), improvement with joint pain (48%), and improvement in diarrhea (29%). Twenty percent of cannabis-using patients reported cannabis use allowed them to decrease the dose of their conventional IBD medications, 13% said they were altogether able to stop using their conventional IBD medications and 4% reported needing to increase their conventional IBD medications. However, it was also noted that prolonged cannabis use (for more than six months at a time), but not intermittent use, to treat IBD symptoms was a strong predictor of requiring surgery in patients with Crohn's disease (OR = 5.03, CI = 1.45 – 17.46), and it was also noted that the OR of prolonged cannabis use approached that of current tobacco smoking (OR = 5.71, 95% CI = 1.92 – 16.98). It was however unclear if the cannabis use preceded or followed the surgery, and as such no temporal associations between cannabis use and need for surgery could be established. Risk of hospitalization for IBD was not associated with cannabis use. Most of the cannabis-using patients experienced side effects associated with cannabis use including anxiety, increased appetite, dry mouth, drowsiness, and euphoria; intensities of effects were rated as mild. The majority (71%) of cannabis-using patients reported not needing to experience euphoria to obtain symptom improvement, while fewer patients (20%) claimed they needed "a high" for beneficial effect. Study limitations included possible referral bias, non-randomized sampling methodology, underestimation of true rate of cannabis use, and patient reporting bias.

Data from clinical studies

A double-blind, randomized, placebo-controlled, crossover clinical study examining the effects of 5 and 10 mg Δ^9-THC in visceral sensitivity reported that Δ^9-THC did not alter baseline rectal perception to experimentally-induced distension or sensory thresholds of discomfort after sigmoid stimulation compared to placebo, in either healthy controls or IBD patients [1229]. However, the authors did note a bias in the patient selection criteria, which could have explained the apparent lack of effect.

A preliminary, observational, open-label, prospective, single-arm clinical 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' QoL, caused a statistically significant increase in subjects' weight, and improved the clinical disease activity index in patients with Crohn's disease [279]. 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. Patients also reported a statistically significant reduction in physical pain, as well as improvement in mental distress. No serious adverse events were noted. Study limitations included study design, subject selection bias, the lack of a proper control group and placebo, small number of subjects, and the inability to establish a dose-response effect.

An eight-week, randomized, double-blind, placebo-controlled pilot clinical study in a group of 21 patients suffering from Crohn's disease reported beneficial effects of smoking cannabis on disease severity [603]. Patients smoked joints containing 0.5 g dried cannabis flowers containing 11.5 mg Δ^9-THC (23% THC, < 0.5% CBD), twice daily, for eight weeks followed by a two week "washout" period. The primary objective of the study was the induction of remission, which was defined as a Crohn's disease activity index (CDAI) score of 150 or less after eight weeks of cannabis treatment. Secondary objectives were response rate (defined as a 100 point reduction in the CDAI), reduction of at least 0.5 mg/dl in C-reactive protein (CRP) levels, or improvement in QoL of at least 50 points as measured by SF-36. All patients were cannabis-naïve and had failed at least one form of medical treatment for the disease, including mesalamine, corticosteroids, thiopurines, methotrexate, or anti-TNF-α. Patients were concomitantly taking other medications during the study period (5-aminosalicylic acid (5-ASA), corticosteroids, purine analogue, methotrexate, opioids, and anti-TNF-α). Although 45% of patients in the study group achieved full remission (CDAI score ≤ 150) compared to 10% of patients in the placebo group, this difference was not statistically significant. Nevertheless, the response rate (CDAI reduction > 100 points) was 90% in the cannabis group and was significantly different from the placebo group. During the two-week washout period, the CDAI score returned to pre-study baseline levels suggesting that the beneficial effects of smoking cannabis were not maintained in the absence of treatment. Patients taking corticosteroids or opioids and assigned to the cannabis group were able to stop using the drugs during cannabis treatment. A statistically significant increase in QoL, measured using the SF-36 QoL instrument, was associated with cannabis treatment but not with placebo. Statistically significant improvements for pain, appetite and in patient satisfaction were reported with cannabis treatment but not with placebo. No significant changes were observed for CRP levels, liver or kidney function, or blood count parameters (e.g. hemoglobin levels, white blood cell count, and hematocrit) between the treatment and placebo groups, although the CRP levels in some individuals in both groups appeared to decrease by 0.5 mg/dl. According to the authors of the study, the reported improvements in disease activity appeared to be symptomatic, with no apparent objective evidence of reduction in inflammatory activity. Principal limitations of this study were the small sample size and a high probability of treatment unblinding. The authors reported the absence of any significant side effects associated with cannabis treatment. Furthermore, no withdrawal symptoms were reported during the two-week washout period.

Note: for **sections 4.9.8.3**, **4.9.8.4**, and **4.9.8.5** below, no clinical studies examining the role of cannabis in the treatment of these disorders have been carried out to date.

4.9.8.3 Diseases of the liver (hepatitis, fibrosis, steatosis, ischemia-reperfusion injury, hepatic encephalopathy)

- ***Pre-clinical studies suggest CB_1 receptor activation is detrimental in liver diseases (e.g. promotes steatosis, fibrosis); while CB_2 receptor activation appears to have some beneficial effects.***
- ***Furthermore, pre-clinical studies also suggest that CBD, THCV and ultra-low doses of THC may have some protective effects in hepatic ischemia-reperfusion injury and hepatic encephalopathy.***

Mounting evidence suggests an important role for the ECS in the pathophysiology of a multitude of diseases affecting the liver with CB_1 and CB_2 receptors playing opposing roles: CB_1 receptor activation is mostly harmful, whereas CB_2 receptor activation is generally protective [35, 1230]. CB_1 receptors are expressed at low levels in the whole liver, hepatocytes, stellate cells, and hepatic vascular endothelial cells, but increased CB_1 receptor expression has been detected in the context of diseases such as hepatocellular carcinoma and primary biliary cirrhosis (reviewed in [1231]) as well as in alcohol-induced liver disease, non-alcoholic fatty liver disease (NAFLD), liver regeneration and fibrogenesis [1230]. CB_2 receptors are undetectable in normal liver but, like the CB_1 receptors, they are upregulated in pathological conditions; these include NAFLD, liver fibrosis, regenerating liver, and hepatocellular carcinoma (reviewed in [1231]). Increases in the concentrations of the endocannabinoids anandamide and 2-AG in the liver appear to vary depending on the pathophysiological condition in question [35].

Steatosis and fibrosis

As mentioned above, CB_1 and CB_2 receptors appear to play *opposing* roles in the liver: activation of the CB_1 receptors is implicated in the progression and worsening of alcoholic and metabolic steatosis, NAFLD, liver fibrogenesis, and circulatory failure associated with cirrhosis; stimulation of the CB_2 receptors, in general, appears to confer beneficial effects in alcoholic fatty liver, hepatic inflammation, liver injury, liver regeneration, and fibrosis (reviewed in [35, 1230] and see also [373-375, 1232]). Conversely, antagonism of the CB_1 receptor appears to attenuate liver fibrosis in animal models by interfering with the production of several pro-fibrotic, pro-inflammatory, as well as anti-inflammatory mediators secreted in the liver during chronic liver injury and the wound healing process [373, 1233].

In vitro studies indicate that CBD may also play a protective role in attenuating liver fibrosis induced by acute liver injury or by chronic alcohol exposure [1234]. CBD dose-dependently triggered the apoptosis of cultured, activated hepatic stellate cells isolated from the livers of rats chronically exposed to an ethanol diet [1234]. The activation of hepatic stellate cells in response to liver injury is considered a key cellular event underlying hepatic fibrogenesis [1234]. Furthermore, CBD dose-dependently promoted the selective apoptosis of activated hepatic stellate cells, but not control hepatic stellate cells or primary hepatocytes, by triggering an endoplasmic reticulum-associated cellular stress response leading to apoptosis; this effect was independent of CB receptor activation [1234].

Ischemia-reperfusion injury and hepatic encephalopathy

Ischemia-reperfusion injury is the main cause of both primary graft dysfunction (i.e. occurring in 10 – 30% of grafts) and primary non-function of liver allograft (i.e. occurring in 5% of grafts) [1235]. Pre-clinical studies indicate a protective role for CBD in hepatic ischemia/reperfusion injury, and hepatic encephalopathy, in mice and rats [1236-1238].

Pre-treatment of mice with 3 or 10 mg/kg body weight CBD (i.p.), 2 h before induction of ischemia-reperfusion in liver, dose-dependently attenuated serum transaminase elevations at 2 and 6 h of reperfusion compared to vehicle [1236]. CBD administered immediately following the induction of ischemia, or at 90 min of reperfusion, still attenuated hepatic injury measured at 6 h of reperfusion, though to a lesser extent than when administered prior to the induction of the ischemia-reperfusion injury. Pre-treatment with CBD also significantly reduced the signs of coagulation necrosis observed 24 h after ischemia-reperfusion, significantly attenuated hepatic cell apoptosis, significantly decreased the expression of pro-inflammatory chemokines and cytokines, attenuated neutrophil infiltration into the injury site, and decreased the expression of markers of tissue and cellular injury.

Similar beneficial findings in a rat model of ischemia-reperfusion injury were reported in a different study; however, CBD (5 mg/kg, i.v.) was administered *after* ischemia-reperfusion injury [1237]. CBD treatment resulted in significant reductions in serum transaminase levels, hepatic lipid peroxidation, and the attenuation of various markers of tissue or cellular injury associated with ischemia-reperfusion.

Administration of Δ^8-THCV (3 or 10 mg/kg, i.p.) 2 h *before* induction of hepatic ischemia-reperfusion injury dose-dependently attenuated serum transaminase elevations at 2 and 6 h of reperfusion compared to vehicle [1239]. Administration of Δ^8-THCV *post-ischemia* attenuated, although to a lesser degree, the hepatic injury measured at 6 h of reperfusion. Pre-treatment with Δ^8-THCV also significantly reduced the extent of coagulation necrosis in the liver, attenuated neutrophil infiltration, decreased the expression of hepatic pro-inflammatory chemokines and cytokines, reduced the hepatic levels of markers of oxidative stress, and decreased the extent of hepatocyte cell death following ischemia-reperfusion injury.

Intraperitoneal administration of CBD (5 mg/kg, i.p.) improved neurological, locomotor, and cognitive functions in a mouse model of fulminant hepatic encephalopathy [1238]. CBD also attenuated the degree of astrogliosis, but did not affect the extent and severity of necrotic lesions in the liver. CBD partially restored whole brain 5-HT levels, as well as the levels of markers of liver function (ammonia, bilirubin, aspartate transaminase – AST, alanine transaminase – ALT) in affected mice.

Lastly, in contrast to high-dose THC (obtained with cannabis smoking or vapourizing), an ultra-low dose of THC (0.002 mg/kg) administered 2 h prior to induction of hepatic ischemia-reperfusion in mice was associated with a significant reduction in hepatic injury as well as significant attenuation of elevations in serum liver transaminases (ALT, AST), hepatic oxidative stress, and acute pro-inflammatory responses (e.g. elevations in TNF-α, IL-1 α, IL-10) [1235].

4.9.8.4 Metabolic syndrome, obesity, diabetes

- ***Pre-clinical studies suggest acute CB_1 receptor activation results in increased fat synthesis and storage while chronic CB_1 receptor activation (or CB_1 receptor antagonism) results in weight loss and improvement in a variety of metabolic indicators.***
- ***Observational studies suggest an association between chronic cannabis use and an improved metabolic profile, while pre-clinical and very limited clinical evidence suggests a potential beneficial effect of THCV on glycemic control (in patients with type II diabetes).***

The endocannabinoid system and energy metabolism

Increasing evidence suggests an important role for the ECS in the regulation of energy balance and metabolism since it exerts regulatory control on virtually every aspect related to search, intake, metabolism, and storage of calories [1240, 1241]. Indeed, the ECS is expressed and functions in a variety of neuronal structures involved in regulating energy balance and metabolism such as the hypothalamus (which modulates energy balance and peripheral metabolism), the cortico-limbic structures (which modulate the hedonic aspects of food intake), and the brainstem (which coordinates central-peripheral communication) [1240, 1241]. Endocannabinoid tone also appears to be modulated by hormones and peptides including leptin, insulin, ghrelin, and corticosteroids [19]. Endocannabinoids, in turn, appear to modulate the release of neurotransmitters and neuropeptides such as opioids, serotonin, and GABA, which are known to play a role in regulating appetite mainly through central mechanisms [1242]. Dysregulation of the ECS is associated with the development of metabolic syndrome and obesity, or conversely anorexia, but may also increase the risk of developing atherosclerosis and type-2 diabetes [12, 19, 1241, 1243].

Pre-clinical studies carried out in animal models of obesity and clinical studies performed in obese humans report increased endocannabinoid tone in adipose tissue, liver, pancreas, and in the hypothalamus compared to controls [1244]. Furthermore, studies have shown that plasma levels of anandamide and 2-AG play different roles in the regulation of eating behaviour; anandamide acts to start the intake of calories, while 2-AG appears responsible for maintaining the nutrient intake beyond physiological needs [1240].

As mentioned above, the regulation of energy balance by the ECS appears to occur both centrally (in the CNS, particularly in the hypothalamus) and peripherally (in multiple organs such as the white adipose tissue, skeletal muscle, pancreas, liver, and small intestine) [12, 19, 1240, 1243, 1245]. In general, overactivity of the ECS (e.g. CB_1 receptor activation) is associated with increased nutrient intake (i.e. increased motivation for palatable food, increase in hedonic properties of palatable food, increased fat preference and intake, increased neural responses to sweet taste, increased odor sensitivity, increased food-seeking behaviour), enhanced energy storage (i.e. increased adipogenesis, decreased fatty acid oxidation, increased glucose uptake, increased insulin secretion, increased liver lipogenesis, decreased liver insulin clearance, decreased liver insulin-induced signaling), reduced energy expenditure (i.e. decreased white adipose tissue lipolysis, decreased mitochondrial biogenesis), and reduced thermogenesis (at the level of brown adipose tissue) [19, 1240, 1241]. Central and peripheral *inhibition* of CB_1 receptor activity, and more generally of the ECS, is beneficial for the treatment of obesity and metabolic disorders [1240].

Pre-clinical data

THC and the role of the CB_1 receptor

In pre-clinical *in vitro* studies, THC significantly inhibited basal and catecholamine-triggered lipolysis in a differentiated mouse adipocyte cell line in a concentration-dependent manner, and caused dose-dependent accumulation of lipid droplets in these cells whereas blockade of CB_1 receptor activation was associated with the opposite effect [25, 1241, 1246-1252].

In mice, activation of the CB_1 receptor resulted in increased *de novo* fatty acid synthesis in the liver and increased formation and storage of triglycerides in the adipose tissue [12, 1253-1255]. In rats, central stimulation of the CB_1 receptor was associated with the development of hepatic and adipose tissue insulin resistance [1244]. Mice lacking overall CB_1 receptor gene expression were hypophagic and were leaner than wild-type mice regardless of diet, had lower plasma insulin levels, did not develop diet-induced insulin resistance or obesity, and had enhanced leptin sensitivity [656, 1252, 1253]. In mice, targeted deletion of the CB_1 receptor in the forebrain-projecting neurons in the hypothalamus and in the nucleus of the solitary tract, and partial deletion in sympathetic neurons were associated with a lean phenotype and resistance to diet-induced obesity (DIO) and increases in plasma levels of leptin, insulin, glucose, free fatty acids, and triglycerides; these effects resulted from an increase in lipid oxidation and thermogenesis as a consequence of enhanced sympathetic tone and a decrease in energy absorption [1256]. Similarly, partial targeted deletion of *CNR1* in the adult mouse hypothalamus lead to a significant decrease in body weight gain triggered by an increase in energy expenditure, rather than a decrease in food intake [1255].

Activation of CB_1 receptors in hepatocytes favours lipid accumulation and causes liver steatosis [1253]. Targeted deletion of *CNR1* in mouse liver is associated with the development of DIO, but retention of glucose, insulin and leptin sensitivity and lipid indices; targeted hepatic re-expression of *CNR1* in *CNR1* knockout mice was associated with glucose intolerance and insulin resistance in response to a high-fat diet, but maintenance of proper body weight [1257, 1258].

Studies with CB_1 receptpr antagonists/inverse agonists strongly suggest that antagonism/inverse agonism at the CB_1 receptor is associated with reduced caloric intake, weight loss, improvement or reversal of hepatic steatosis, and restoration of insulin and glucose sensitivity and normal lipid indices in various animal models of DIO [656, 1259-1265]. Clinical studies with the CB_1 receptor antagonist rimonabant have strongly supported the data gathered from animal studies [1266-1272]. Muscle endocannabinoid levels and muscle CB_1 receptor expression also appear to be altered by consumption of a high-fat diet, and in obesity [1241, 1273]. Furthermore, activation of the ECS inhibits oxidative pathways and mitochondrial biogenesis [1241, 1274].

An animal study that investigated the effects of *chronic* THC administration on body weight gain and gut microbiota in mice reported that chronic daily treatment of DIO or lean mice with THC (dose = 2 mg/kg for three weeks and 4 mg/kg for one additional week) was associated with a reduction in weight and fat mass, as well as a reduction in energy intake in DIO mice, but not in lean mice [1275]. Furthermore, the changes in gut microflora normally observed in DIO mice were prevented with the administration of THC. The change in body weight, fat mass, and daily energy intake appeared to be dose-dependent, with the 4 mg/kg dose being significantly more effective than the 2 mg/kg dose. DIO mice did not show any effect of THC over time on locomotor activity or altered gut transit at any of the tested doses of THC. In DIO mice, the high-fat diet led to an increase in the Firmicutes : Bacteroidetes ratio that was prevented by THC treatment. Furthermore, THC increased abundance of *Akkermansia muciniphila* spp. which has been implicated in controlling fat storage and adipose tissue metabolism leading to weight loss.

Taken together, the above findings suggest an important role for the CB_1 receptor, both centrally and peripherally, in regulating energy balance; acute stimulation of the CB_1 receptor promotes energy storage and lipogenesis, whereas CB_1 receptor antagonism or chronic CB_1 receptor agonism have the opposite effects. Consistent with some of these findings, acute administration of cannabis and prescription cannabinoids (dronabinol, nabilone) are known to increase appetite and body weight and have been used clinically to treat HIV/AIDS-associated anorexia-cachexia, and possibly also cancer-associated cachexia (see **Sections 4.4.1** and **4.4.2**, respectively).

Observational studies

In contrast to the effects of acute CB_1 receptor agonism (e.g. acute THC exposure), studies examining the effects of *chronic* cannabis use on body weight and metabolic status in non-clinical populations have found the opposite effects.

One cross-sectional, case-control study that examined 30 cannabis smokers and 30 control subjects for any association between cannabis smoking and abdominal fat area, hepatic steatosis, insulin resistance, reduced β-cell function or dyslipidemia reported that chronic cannabis smoking was associated with a statistically significant lower total abdominal fat area and a lower subcutaneous abdominal fat area while no difference was noted for abdominal visceral fat area [1276]. However, chronic cannabis smokers showed a relative statistically significant increase in percentage of visceral fat compared to controls. Furthermore, chronic cannabis smoking was not associated with hepatic steatosis, insulin insensitivity, impaired pancreatic β-cell function or glucose intolerance. Median self-reported duration of cannabis use was 12 years (range: 2 – 38 years) and median number of joints smoked per day was 9.5 (range: 3 – 30). Percentage of visceral fat was not related to age, frequency or duration of cannabis use. Hepatic fat content was also not different between the cannabis and control groups and was not related to age, frequency, or duration of cannabis use. Fasting levels of glucose, insulin, total cholesterol, LDL cholesterol, triglycerides or free fatty acids were not different between control and cannabis users.

Other studies report that the prevalence of obesity appears to be significantly lower in cannabis users than in non-users, and the proportion of obese individuals also appeared to decrease with frequency of cannabis use according to a cross-sectional analysis of two U.S. epidemiological studies [1277]. In one study, the investigators examined data from the **NESARC** and the **NCS-R**eplication (**NCS-R**) which are two face-to-face surveys of adults ages 18 years and older from the civilian non-institutionalized population residing in the United States. The **NESARC** counts 43 093 respondents (response rate 81%), while the **NCS-R** is an independent survey that counts 9 282 respondents (response rate 73%). The adjusted prevalence of obesity was 22% and 25% in participants who reported no cannabis use in the past 12 months in the **NESARC** and **NCS-R** respectively [1278]. However, the adjusted prevalence of obesity was 14% and 17% in participants reporting the use of cannabis three days per week or more in the **NESARC** and the **NCS-R** respectively [1278]. After adjusting for sex and age, as well as other drug use, the use of cannabis was associated with BMI differences in both samples.

Data from the **NHANES III**, (1988 – 1994), a cross-sectional survey of 10 896 adults, reported that current marijuana users had a lower age-adjusted prevalence of diabetes mellitus compared to non-marijuana using adults (OR = 0.42, 95% CI = 0.33 – 0.55) [1279]. Furthermore, the prevalence of elevated C-reactive protein was significantly higher among non-marijuana users (18.9%) than among past (13%), current light (16%), or heavy (9%) marijuana users. The lower odds of diabetes mellitus among marijuana users was statistically significant (OR = 0.36, 95% CI = 0.24 to 0.55). A meta-analysis of eight replication samples from large U.S. epidemiological studies, **NHANES** (2005 – 2012) and the **N**ational **S**urvey on **D**rug **U**se and **H**ealth (**NSDUH**, 2005 – 2012), supported these findings, reporting that recently active cannabis smoking and diabetes mellitus are inversely associated, with an OR of 0.7 (95% CI = 0.6 – 0.8) [1280].

Another study looking at 4 657 adult men and women from the **NHANES** (2005 – 2010) found that current marijuana use was statistically significantly associated with a smaller waist circumference, as well as 16% lower fasting insulin levels and 17% lower insulin resistance (homeostatic model assessment of insulin resistance, HOMA-IR) [1281].

Another study that sought to determine the relationship between cannabis use, obesity, and insulin resistance based on data from 786 Inuit adults from the 2004 Nunavik Inuit Health Survey reported that cannabis use was highly prevalent in the study population (57%) and was statistically associated with a lower BMI, lower percentage fat mass, lower fasting insulin, and lower insulin resistance score (HOMA-IR) [1282]. In multivariate analysis, past-year cannabis use was associated with a 0.56 lower likelihood of obesity (95% CI = 0.37 – 0.84).

A review of cannabis use and cardiometabolic risk found a lower BMI and decreased fasting insulin, glucose, insulin resistance and prevalence of diabetes among current cannabis users [1283].

Taken together, the above studies suggest an association between chronic cannabis use and an improved metabolic profile (i.e. lower BMI, lower fasting insulin, lower insulin resistance score, lower likelihood of obesity, lower prevalence of diabetes mellitus).

Role of the CB_2 receptor

The CB_2 receptor also appears to play an important role in energy balance [1284]. Pre-clinical studies in mice indicate that the CB_2 receptor is expressed in epididymal adipose tissue in lean mice, and the levels of this receptor appear to increase in the non-parenchymal cell fractions of adipose tissue and liver in genetically obese mice or in wild-type mice fed a high-fat diet [1284]. Furthermore, systemic administration of a CB_2 receptor-selective agonist to lean or obese mice, or exposure of cultured fat pads to the same agonist, was associated with upregulation of a subset of genes linked to inflammation in the adipose tissue but not the liver [1284]. Conversely, administration of a CB_2-selective antagonist reduced inflammation both in adipose tissue and in liver of obese animals. Under a high-fat diet, mice lacking the CB_2 receptor displayed a slower body weight progression and were more insulin sensitive than wild-type mice. CB_2 knockout mice on a high-fat diet also exhibited minimal hepatic steatosis compared to wild-type mice. Mice deficient in CB_2 receptor expression also exhibited increased food intake and body weight with age compared to wild-type mice [1285]. The CB_2 receptor knockout mice did not develop insulin resistance and showed enhanced insulin-stimulated glucose uptake in skeletal muscle.

Another study that examined the role of the CB_2 receptor in obesity found that mice lacking CB_2 receptor expression showed age-dependent obesity with hypertrophy of the visceral fat, immune cell polarization toward pro-inflammatory subpopulations in fat and liver, and hypertension as well as increased mortality despite normal blood glucose [1286]. These mice also developed stronger paw inflammation. These effects did not result from overeating or lack of physical activity. Conversely, CB_2 receptor agonism in wild-type littermates fed a high-fat diet prevented diet-induced hypertension, and also reduced diet-induced pro-inflammatory immune responses but did not reduce weight gain. Taken together, these results suggest an important and complex role for the CB_2 receptor in energy balance and obesity, and further studies are needed to better understand its role.

Other cannabinoids

Pure Δ^9-THCV administered intraperitoneally (3 mg/kg, 10 mg/kg, or 30 mg/kg) in mice suppressed feeding and significantly reduced body weight gain, but this effect appeared to be blocked with a botanical extract containing both Δ^9-THCV and Δ^9-THC [113]. Inclusion of CBD into the botanical extract, as a way of attenuating the proposed hyperphagic effects of THC in this study, resulted in a trend towards decreased food intake in treated mice, but the effect did not reach statistical significance.

In another study, chronic administration of 5 mg/kg and 12.5 mg/kg THCV in mice with DIO was associated with a statistically significant reduction of body fat mass but not total body weight [1287]. THCV at the highest tested doses (5 and 12.5 mg/kg) also tended to increase energy expenditure. Additionally, THCV dose-dependently improved plasma fasting glucose and glucose tolerance following challenge and improved insulin sensitivity (i.e. fasting plasma insulin and insulin response). Administration of THCV was also associated with a reduction in liver triglyceride levels.

Lean and obese rats injected with a cannabis extract (on alternate days, for 28 days) containing a THC : CBN : CBD ratio of 1.0 : 1.2 : 0.4 (5 mg/kg Δ^9-THC) exhibited a significant reduction in weight gain during the study period, but the cannabis extract treatment was not associated with any changes in either insulin or glucose levels [1288].

A randomized, double-blind, placebo-controlled, parallel group pilot study investigated the efficacy and safety of CBD, THCV and combination treatment on glycemic and lipid parameters in patients with type II diabetes [1289]. In this clinical study, 62 patients were randomized to five treatment arms: CBD (100 mg b.i.d.), THCV (5 mg b.i.d.), 1 : 1 ratio of CBD and THCV (5 mg : 5 mg b.i.d.), 20 : 1 ratio of CBD to THCV (100 mg : 5 mg b.i.d) or matched placebo for 13 weeks. Compared to placebo, THCV significantly decreased fasting plasma glucose and improved pancreatic β-cell function, improved adiponectin levels, and apolipoprotein A levels although plasma HDL levels were unaffected. Compared with baseline, CBD decreased resistin and increased glucose-dependent insulinotropic peptide and none of the combination treatments had a significant impact on end points. Furthermore, CBD and THCV appeared to be well tolerated. The majority of patients experienced adverse events that were mild to moderate in severity but the incidence of adverse events was similar between all treatment groups. Decreased appetite was the most commonly reported adverse event in all the groups except the 20 : 1 CBD : THCV group. The authors suggest that THCV could represent a new therapeutic target in glycemic control in subjects with type II diabetes.

4.9.8.5 Diseases of the pancreas (diabetes, pancreatitis)

- ***Pre-clinical studies in experimental animal models of certain cannabinoids in the treatment of acute or chronic pancreatitis are limited and conflicting.***
- ***Limited evidence from case studies suggests an association between acute episodes of heavy cannabis use and acute pancreatitis.***
- ***Limited observational studies suggest an association between chronic cannabis use and lower incidence of diabetes mellitus.***
- ***One small clinical study reported that orally administered THC did not alleviate abdominal pain associated with chronic pancreatitis.***

Function of the endocannabinoid system in the pancreas

Although there appears to be a general lack of consensus as well as insufficient information regarding the exact expression, distribution, and function of the various ECS components in the pancreas among different species, the pancreas does appear to have at least some, and in certain cases many, of the individual elements of the ECS [1242, 1290, 1291].

Two studies using primary human islet cells suggest that the CB_1 and CB_2 receptors are expressed in these cells, and that stimulation of the CB_1 receptor is associated with secretion of insulin and glucagon while stimulation of the CB_2 receptor is associated with either increased or decreased insulin secretion [1242, 1290, 1292]. More recently, the endocannabinoid 2-AG has been implicated in the regulation of both insulin and glucagon secretion in human pancreas [1291].

Intra-muscular administration of cannabis resin (containing 6.3% Δ^9-THC, 3.2% CBD, and 1.9% CBN) at increasing doses (Δ^9-THC at 2.5, 5.0, and 10 mg/kg) to dogs was associated with a progressive increase in plasma glucose levels which reached maximum values 90 min after administration, with a return to baseline values 180 min after administration [1293]. Injection of anandamide or a CB_1 receptor-selective agonist in rats was associated with acute glucose intolerance, whereas administration of a CB_1 receptor inverse agonist attenuated this effect [1294]. 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 [1295].

Survey data

A cross-sectional study of 10 896 adults, ages 20 to 59, who were participants in the **NHANES III**, 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 [1279]. 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. 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.

Cannabis, the endocannabinoid system, and acute and chronic pancreatitis

Acute, heavy cannabis use has been linked to the development of acute pancreatitis [377-381]. A recent systematic review of cannabis-induced acute pancreatitis suggests increased prevalence mainly amongst younger patients under 35 years of age [381]. Furthermore, subsequent causality analysis suggests that cannabis may be a possible risk factor for toxin-induced acute pancreatitis. 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 [1296, 1297]. 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 [1296].

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 [1297]. In addition, in contrast to the findings obtained for acute pancreatitis [1296], tissues isolated from patients with chronic pancreatitis appeared to have decreased levels of both anandamide and 2-AG [1297]. 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 [1297].

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.

Elevations in the plasma levels of anandamide have been noted in a rat model of severe acute pancreatitis [1298], and administration of the CB_1 receptor antagonist AM251 after induction of pancreatitis appeared to improve the course of the disease [1298]. 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 [1299]. 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 [1300]. 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 [1296]. 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 [1301]. 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.

Clinical data
A randomized, single dose, double-blinded, placebo-controlled, two-way, cross-over clinical study in 24 patients (sub-divided into daily opioid and non-opioid users) suffering from abdominal pain associated with chronic pancreatitis examined the analgesic efficacy, pharmacokinetics and tolerability of orally-administered 8 mg THC or active placebo (5 or 10 mg diazepam) in a double-dummy design [595]. The study reported a lack of efficacy with THC in reducing chronic pain associated with chronic pancreatitis but good tolerance with only mild or moderate adverse events. No differences were noted between THC and diazepam in VAS measures of alertness, mood, and calmness but THC was associated with a significant increase in anxiety compared to diazepam. Heart rate was also significantly increased with THC compared to diazepam. Most frequent adverse events associated with THC were somnolence, dry mouth, dizziness and euphoric mood. No serious adverse events were noted. Pharmacokinetic parameters of THC were similar between opioid and non-opioid users and showed a delayed absorption and increased variability compared to healthy volunteers. Study limitations included small number of study subjects, short trial duration, single dose design, and low dosage of THC.

4.9.9 Anti-neoplastic properties

- ***Pre-clinical studies suggest that certain cannabinoids (THC, CBD, CBG, CBC, CBDA) often, but not always block growth of cancer cells in vitro and display a variety of anti-neoplastic effects in vivo, though typically at very high doses that would not be seen clinically.***
- ***While limited evidence from one observational study suggests cancer patients use cannabis to alleviate symptoms associated with cancer (e.g. chemosensory alterations, weight loss, depression, pain), there has only been one limited clinical study in patients with glioblastoma multiforme, which reported that intra-tumoural injection of high doses of THC did not improve patient survival beyond that seen with conventional chemotherapeutic agents.***

A number of studies have implicated the ECS 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 strategy in controlling the malignancy of different cancers — dysregulation of the ECS is associated with carcinogenesis

[1302, 1303].

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 [1206, 1304-1308]. Furthermore, 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 [1303]). 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 ECS in cancer and are likely to pose challenges to potential therapeutic approaches. Nonetheless, a large 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 [1303, 1309]).

In some *in vitro* studies, the anti-neoplastic effects of Δ^9-THC appear to be biphasic: lower doses (under 100 nM) are considered pro-proliferative; higher doses (above 100 nM) are thought to be anti-proliferative [1310], although many exceptions have been noted. Furthermore, cannabinoid concentrations above 100 nM, that is one to two orders of magnitude above the average affinity of these receptors for cannabinoids, are likely to produce off-target, cannabinoid receptor-independent effects [1311]. 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 [227]. These concentrations correspond to concentrations of 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 [227], respectively, corresponding to 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 60 nM [420]. 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 Δ⁹-THC following smoking*). Such Δ^9-THC plasma concentrations correspond to 160 and 320 nM Δ^9-THC, respectively. Plasma concentrations of Δ^9-THC are also known to vary widely across individuals, and diminish more rapidly when cannabis (or Δ^9-THC) is smoked compared to when cannabis (or Δ^9-THC) is ingested orally. 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. These values represent estimative comparisons as the actual tissue concentrations of cannabinoids are likely to vary significantly both within and across individuals, among varying routes of administration and cell types; and micro-environments *in vitro* and *in vivo* are conceivably different.

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 [1312]. 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 [1313]. In the case of breast cancer, Δ^9-THC reduced human breast cancer cell proliferation at concentrations of 4 to 10 μM, with more aggressive estrogen receptor-negative tumour cells being more sensitive to the effects of THC [1314]. In apparent contrast, another study showed that Δ^9-THC (50 μM *in vitro* or 50 mg/kg *in vivo*) enhanced breast cancer growth and metastasis even though the breast cancer cells did not express detectable levels of CB receptors suggesting a CB_1 receptor-independent mechanism of action [1315]. Furthermore, Δ^9-THC, CBD, and CBN all stimulated breast cancer cell proliferation at concentrations ranging from 5 to 20 μM [1316], 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 CBG, CBC, CBDA, and THCA 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 [1317]. In *in vitro* studies examining the role of cannabinoids in lung cancer, Δ^9-THC (10 – 15 μM) attenuated growth factor-induced migration and invasion of non-small cell lung cancer cell lines [1318]. In the case of colorectal cancer, Δ^9-THC at concentrations of 2.5 μM and above (range: 7.5 – 12.5 μM) were associated with a decrease in colorectal cancer cell survival, whereas lower concentrations (100 nM – 1 μM) had no effect [1319]. An *in vitro* study examining the role of THC in skin cancer reported that 5 and 10 μM THC had no effect on cell proliferation of HCmel12 or B16 skin cancer cells [1320]. Another *in vitro* study examining the anti-neoplastic effects of CBG on colon carcinogenesis found that CBG (3 – 30 μM) inhibited colon cancer cell viability but this effect was both time and environment-dependent [1321]. Another study reported that a CBD botanical extract (66% CBD, 2.4% THC, 1.0% CBG, 0.9% CBDV, 0.3% CBDA, 0.1% CBN) as well as pure CBD (at concentrations of 1 – 5 µM) did not affect viability of colorectal cancer cells (DLD-1 and HCT116) [1322]. However, the CBD botanical extract and pure CBD exerted anti-proliferative effects on these colon cancer cells, but not on healthy cells [1322]. One other *in vitro* study assessed the anti-proliferative effect of CBD and THC used alone and in combination with radiotherapy [1323]. In this study, treatment of two human and one murine glioma cell line with pure CBD, THC, or two cannabinoid botanical drug substances (BDS) enriched in either CBD or THC (CBD BDS = 64% CBD, 3.6% THC, 1.1% CBG, 5.2% CBC, 1.3% CBDV, 0.4% CBDA; or THC BDS = 65% THC, 0.4% CBD, 1.3% CBG, 1.8% CBC, 0.9% THCV, 0.4% THCA, 2% CBN, and 0.2% cannabitriol) was associated with a reduction in cell numbers in all three cell lines in a dose-dependent manner [1323]. A dose of approximately 10 µmol/L for all tested substances was associated with a 50% reduction in cell numbers (IC_{50}). Combining pure THC and pure CBD was associated with a hyper-additive inhibitory effect on cell numbers. In additional experiments, pre-treatment of the three glioma cell lines with a combination of pure THC and CBD (10 µmol/L of each) along with irradiation was associated with a slowing of DNA double-strand break repair and a trend towards increased cell death [1323]. In another study, the anti-leukemic efficacy of THC was examined in several leukemia cell lines and native leukemia blasts cultured *ex vivo* [1324]. THC produced significant and dose-dependent inhibition of cellular proliferation with an IC_{50} of 15 µM in a T-lymphoblastic leukemia cell line and with an IC_{50} of 18 µM in an acute myeloid leukemia cell line. Higher doses were associated with apoptosis that was CB_1 and CB_2 receptor-dependent. THC treatment of myeloid leukemia and lymphatic leukemia blasts cultured from patients and grown *ex vivo* was associated with a reduction in the number of viable cells [1324].

Taken together, these and other *in vitro* studies suggest that cannabinoids often, but not always, exert growth-inhibiting actions on cultured cancer cells and can have complex biological effects in the context of malignancies. Differences in experimental conditions, cancer cell type, cell growth environment, 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 significantly (i.e. one to four orders of magnitude) higher than the concentrations of Δ^9-THC seen when it is taken 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 [1325]. Furthermore, no substantial change was observed in certain behavioural measures suggesting that the effect of Δ^9-THC was limited to diseased neural tissues. 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 [1326]. Δ^9-THC, at doses of 5 mg/kg/day, administered intraperitoneally 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 [1318]. CBD (5 mg/kg) or CBD-rich extract (6.5 mg/kg) administered intra-tumourally or intraperitoneally, twice per week, to breast-cancer-cell-xenografted athymic mice significantly decreased both tumour volume and the number of metastatic nodules [1317]. Other investigators showed that intraperitoneal 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 [1327]. Importantly, the primary tumour acquired resistance to the inhibitory properties of CBD by day 25 of treatment. An *in vivo* study that evaluated the anti-tumour efficacy of biodegradable polymeric microparticles allowing controlled release of THC (25 mg administered, 10 mg released) and CBD (27 mg administered, 11 mg released) into glioma xenografts showed a significant reduction in glioma growth. These doses are far higher than could be achieved by systemic administration of these cannabinoids and would also be associated with significant psychoactive effects [1328]. An *in vivo* study examining the anti-neoplastic effects of CBG on colon carcinogenesis found that CBG (3 and 10 mg/kg CBG) inhibited xenografted colon cancer cell growth by 45% [1321]. An *in vivo* study assessing the effect of a CBD botanical extract on colorectal cancer reported that a daily injection of the extract (5 mg/kg, i.p.) significantly lowered average tumour volume, but that effect was only maintained for seven days after which time no differences in tumour size were observed between the experimental and control groups [1322]. One study examined the effect of combining THC, CBD and radiotherapy in a mouse model of glioma [1323]. In this study, combining THC and CBD (100 µmol/L each) was associated with a reduction in tumour progression and further addition of irradiation to the combination cannabinoid treatment was associated with further reduction in tumour growth [1323]. An *in vivo* study of the effects of THC in skin cancer reported that doses of 5 mg/kg THC/day (s.c.) significantly reduced the growth of HCmel12 melanomas but not B16 melanomas [1320]. Furthermore, the anti-neoplastic effect was found to be CB receptor-dependent. Lastly, review of the *in vivo* anti-neoplastic activity of CBD reported that chronic systemic administration of CBD at doses in the range of 1 – 5 mg/kg was associated with anti-metastatic activity, while doses between 15 and 25 mg/kg of CBD administered systemically and 10 mg/kg CBD administered orally were needed to limit tumour progression in mouse xenograft model that more closely resemble primary tumour growth [1329]. Furthermore, doses of THC and CBD of 4 mg/kg each delivered systemically and 100 mg/kg CBD delivered orally were reported to sensitize tumours to first line agents in mouse xenograft models that more closely resemble primary tumour growth [1329]. Taken together, these studies suggest that cannabinoids such as Δ^9-THC and CBD can, at least under a specific set of circumstances, have anti-neoplastic effects in various animal models of cancer at certain dose 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 [1330]. Likewise, combining sub-maximal doses of Δ^9-THC with temozolomide reduced the *in vitro* viability of several human glioma cell lines and primary cultures of glioma cells derived from human glioblastoma multiforme biopsies [1331]. 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 [1331]. These studies suggest that cannabinoids might sensitize certain tumours to the anti-neoplastic action of conventional chemotherapeutic drugs.

Observational and clinical data

A non-randomized, cross-sectional survey and retrospective chart review of 15 patients (mostly male) with a history of head and neck cancer treated with radiotherapy or chemotherapy who had also used cannabis for medical purposes examined patient characteristics and stated reasons for use of cannabis for medical purposes to manage long-term head and neck cancer treatment-related morbidities [1332]. The study revealed that most of the survey participants reported smoking cannabis while fewer reported ingestion, vapourization, and use of homemade concentrated oil. The majority of the patients reported using cannabis daily or more frequently. Cannabis was reported to provide benefit in altered sense, weight maintenance, depression, pain, appetite, dysphagia, xerostomia, muscle spasms, and sticky saliva as side effects of radiotherapy.

A case report of two children with septum pellucidum/forniceal pilocytic astrocytomas noted spontaneous regression of the tumours during the same period that cannabis was consumed via inhalation (reported frequency of three times per week to daily, strength and composition unknown) [1333]. The patients did not receive any adjuvant treatment following surgery and were followed-up post-operatively over the course of a number of years; regression of the tumours appeared to coincide with cannabis use that according to the authors raises the possibility that cannabis may have played a role in tumour regression.

There is only one report of a clinical study of Δ^9-THC to treat cancer [1334]. In this non-placebo controlled pilot study, nine patients with glioblastoma multiforme who had failed to respond to standard surgical and radiation therapy, had clear evidence of tumour progression, and had a minimum Karnofsky score of 60, were treated with 20 to 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. Intra-tumoural administration of Δ^9-THC appeared to be well tolerated and the effect of Δ^9-THC on patient survival was similar to that observed in other studies using chemotherapeutic agents such as temozolomide or carmustine [1335, 1336]. Administration of Δ^9-THC reduced the expression of some molecular markers of glioblastoma multiforme progression in tumour specimens obtained from treated patients [1330, 1334, 1337] and *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 [1334, 1338]. 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 [1338].

Despite the evidence presented in these and other studies, there is some concern regarding the use of Δ^9-THC in anti-tumoural strategies, especially if it is administered systemically because of its high hydrophobicity, relatively low agonist potency, and its well-known psychoactive properties [1303, 1339, 1340]. Much also remains to be known about 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 [1317, 1339]. Lastly, the apparent biphasic effect of cannabinoids further highlights the need for more comprehensive dose-response studies [1341].

4.9.9.1 Emerging potential therapeutic uses

Atherosclerosis

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 [1342-1344]. 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 [1342]. 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. These findings were supported by another study that showed that intraperitoneal administration of a synthetic CB_1/CB_2 receptor agonist significantly reduced aortic plaque area in the ApoE knockout mouse [1344]. Administration of the cannabinoid receptor agonist reduced macrophage adhesion and infiltration into the atherosclerotic plaque, as well as reducing the expression of vascular cellular adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), and P-selectin in the aorta. Again, the observed beneficial effects appeared to result from activation of the CB_2 receptor. 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 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 [1345]. 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 [1346]. 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 [1347]. 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. On the other hand, activation of the CB_1 receptor is associated with the release of reactive oxygen species and endothelial cell death [1348], 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 [1343]. 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 [1343, 1345, 1348-1350] although some uncertainty still remains regarding the exact role played by the CB_2 receptor [1351]. CBD has also been shown to potently inhibit the activity of the enzyme 15-lipoxygenase, which has been implicated in the pathophysiology of atherogenesis [1349, 1352]. 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 (e.g. Cesamet®), nabiximols (e.g. Sativex®) or dronabinol (e.g. Marinol®, no longer available in Canada)) also apply to those considering using cannabis, especially THC-predominant cannabis. Healthcare professionals may also wish to consult the College of Family Physicians of Canada preliminary guidance document on authorizing dried cannabis for medical purposes[586] and the recent simplified guideline for prescribing medical cannabinoids in primary care [587].

The risk/benefit ratio of using cannabis (especially THC-predominant 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**. Consult **Figure 3** for additional guidance.

- Cannabis (especially cannabis administered by smoking or vapourization) containing primarily THC (and especially higher levels of THC with little if any CBD) should not be used in any person under the age of 25 [540, 1106], unless the benefit/risk ratio is considered by the physician to be favourable. The adverse effects of (THC-predominant) cannabis use on mental health are greater during development, particularly during adolescence (ages 10 to 24), than in adulthood with risks increasing with younger age, frequent use and THC potency [151, 182, 198, 205, 541, 1116, 1120] (see **Section 7.7.3**). Emerging evidence suggests a statistically significant association between use of ultra-high potency cannabis concentrates such as BHO with higher levels of physical dependence [520].
- Cannabis should not be used in any patient who has a history of hypersensitivity to any cannabinoid or to smoke (if cannabis will be smoked) [365, 366, 393, 394, 1353, 1354] (see **Section 7.3**).
- Cannabis should not be used in patients with severe cardiovascular or cerebrovascular disease because of occasional hypotension, possible hypertension, syncope, tachycardia, myocardial infarction and stroke [141, 180, 353, 354, 1355-1357] (see **Section 7.5**).
- Smoked cannabis is generally not recommended in patients with respiratory disease (e.g. insufficiency such as asthma or chronic obstructive pulmonary disease) [364, 365] (see **Section 7.2**).
- Cannabis should not be used in patients with severe liver or renal disease. In patients with ongoing chronic hepatitis C, daily cannabis use has been shown to be a predictor of steatosis severity in these individuals [34, 1358] (see **Section 7.6.2**).
- Cannabis containing primarily THC (with little if any CBD), and especially higher levels of THC, should not be used in patients with a personal history of psychiatric disorders (i.e. psychosis, schizophrenia, anxiety and mood disorders), or a familial history of schizophrenia [183, 1085] (see **Section 7.7.3**).
- 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 [1078, 1359, 1360] (see **Sections 2.4** and **4.9.5.4**).
- 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 [219-221] (also see **Section 7.7**). Cannabis may also exacerbate the CNS depressant effects of alcohol and increase the incidence of adverse effects and driving impairment (see **Section 7.7.2**). Patients should be advised of the negative effects of psychoactive cannabis/cannabinoids on memory, cognitive and psychomotor skills and to report any mental or behavioural changes that occur after using cannabis [233, 234].
- Cannabis is not recommended in women of childbearing age not on a reliable contraceptive, as well as those planning pregnancy, and those who are pregnant, or breastfeeding [61, 1361, 1362] (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 [145, 190, 329, 1363, 1364]. The drug has complex effects in the CNS and can cause cognitive and memory impairment, changes in mood, altered perception, and decreased impulse control among many other effects [235, 1365-1367].

Patients should be supervised when administration is initiated and should be monitored on a regular basis.

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 potency of the product, its processing, and by different smoking and vapourizing 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 or vaping liquid is vapourized. Dosing should begin at lowest possible dose to maximize potential therapeutic effects and minimize risks of adverse effects. Smoking or vapourization should proceed slowly and cautiously in a gradual fashion (with sufficient time between puffs/inhalations to gauge effects – e.g. 30 min) 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 peak at 3 – 4 h, 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 with sufficient time between doses in order to gauge the effects and to prevent overdosing [227, 405] (see **Section 3.0**).

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 [165, 173, 508, 1368] (see **Section 7.7.3.2**) .

Occupational hazards: Patients using cannabis/cannabinoids 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 significantly decrease their ability to perform such tasks [154, 155, 204, 229, 240, 495, 1369]. Depending on the dose, the route of administration and the frequency of use, impairment can last for over 24 h after last use because of the long half-life of Δ^9-THC [78, 152, 431, 1370, 1371]. Furthermore, impairment can be exacerbated with co-consumption of other CNS depressants (e.g. benzodiazepines, barbiturates, opioids, anti-histamines, muscle relaxants, or ethanol [159, 219, 220, 227, 1372-1375] (see **Section 7.7.2**).

Pregnancy: Pre-clinical studies suggest that multiple components of the endocannabinoid system as well as endocannabinoid tone play a critical role in fertilization, oviductal transport, implantation, and fetal/placental development (reviewed in [1376-1378]). In fact, CB_1 and CB_2 receptors are expressed (proteins) in rodent and human ovarian tissue, oviduct, uterus and testis [1378]. These receptors are also detected (proteins) in oocytes at all stages of maturation [1378]. Furtherrmore, CB_1 receptor mRNA is expressed from the four-cell stage through the blastocyst stage, while CB_2 receptor mRNA is expressed from the one-cell stage to the blastocyst stage [1379]. High circulating levels of anandamide have been associated with an increased incidence of miscarriage [1380]. In addition, there is a risk that maternal exposure to cannabis or cannabinoids could potentially adversely affect conception and/or maintenance of pregnancy. However, two recent systematic reviews and meta-analyses reported mixed conclusions about the harms to neonatal health with cannabis use *in utero* [1361, 1362]. Nevertheless, it may be prudent to avoid the use of cannabis during pregnancy as there is evidence of reduced neonatal birthweight and long-term developmental problems in children exposed to cannabis *in utero* [1381-1384]. THC readily crosses into the placenta [1384]. CB_1 receptors are expressed (proteins) in germ cells, from spermatogonia to spermatozoa, and Leydig cells, while CB_2 receptors (proteins) are expressed in Sertoli cells [1378].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 [396] (see **Section 7.4**).

Lactation: Cannabinoids are excreted in human milk and may be absorbed by the nursing baby [1385, 1386]. Because of potential risks to the child, nursing mothers should not use cannabis.

6.1 Tolerance, dependence, and withdrawal symptoms

Tolerance, and psychological and physical dependence can occur with prolonged use of cannabis [181, 324, 329]. Dependence develops slowly and appears more likely with higher, more frequent dosing [336, 337, 510, 512]. Emerging evidence suggests use of ultra-high potency cannabis concentrates such as BHO is associated with greater levels of physical dependence [520]. See **Section 2.4** for further information on tolerance, dependence, and withdrawal symptoms.

6.2 Drug interactions

Drug interactions involving cannabis and cannabinoids can be expected to vary considerably in their clinical significance given the wide variability in products, potencies, ratios of THC and CBD, doses, routes of administration, populations using cannabinoids and other factors [468]. However, some of the more clinically significant interactions may occur when cannabis is taken with other CNS depressant drugs such as sedative-hypnotics or alcohol [159, 219-221, 1373-1375, 1387, 1388]. 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 [227, 431].

Xenobiotic-mediated inhibition or potentiation of cannabinoid metabolism

Δ^9-THC is oxidized by the xenobiotic-metabolizing CYP mixed-function oxidases 2C9, 2C19, and 3A4 into approximately 80 metabolites [78, 468,]. Therefore substances that *inhibit* these CYP isoenzymes such as certain anti-depressants (e.g. fluoxetine, fluvoxamine, moclobemide, and nefazodone), proton pump inhibitors (e.g. cimetidine and omeprazole), macrolides (e.g.arithromycin, erythromycin, telithromycin, troleandomycin), anti-mycotics (e.g. itraconazole, fluconazole, ketoconazole, miconazole, voriconazole, posaconazole), calcium antagonists (e.g. diltiazem, verapamil), HIV protease inhibitors (e.g. ritonavir, indinavir, nelfinavir, saquinavir, telaprevir, atazanavir, boceprevir, lopinavir), amiodarone, conivaptan, sulfaphenazole, azamulin, ticlopidine, nootkatone, grapefruit juice, mibefradil, and isoniazid *can potentially increase the bioavailability* of Δ^9-THC (and metabolites such as 11-hydroxy-THC) as well as the risk of experiencing THC- and 11-hydroxy-THC-related side effects [422, 468, 470, 1389]. Additive tachycardia, hypertension, and drowsiness have been reported with THC and concomitant consumption of tricyclic antidepressants such as amytryptiline, amoxapine, and desipramine [227]. Additive hypertension, tachycardia, and possible cardiotoxicity have been reported with THC and concomitant consumption of sympathomimetic agents such as amphetamines and cocaine [227]. Additive or supra-additive tachycardia and drowsiness have been reported with THC and concomitant consumption of atropine, scopolamine, antihistamines, or other anti-cholinergics [227]. Reversible hypomanic reaction has been reported with concomitant consumption of THC with disulfiram [227].

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, avasimibe, and Saint John's Wort may conversely *decrease the bioavailability* of THC and CBD and hence their effectiveness if used in a therapeutic context [422, 468, 470, 1389].

Like THC, CBD is also metabolized by CYP 2C19 and 3A4 but could also act as a potential substrate for CYP 1A1, 1A2, 2C9, 2D6, 2E1, and 3A5 [468]. As such, the bioavailability of CBD could potentially be increased by many of the same substances listed for THC, as well as buproprion, paroxetine, quinidine, clomethiazole, diallyl, disulfide, diethyldithiocarbamate, and disulfiram [468].

CBN is metabolized by CYP 2C9 and 3A4 but could also act as a potential substrate for CYP 2C19 [468].

The Sativex® product monograph cautions against combining Sativex® with amitriptyline or fentanyl (or related opioids) which are metabolized by CYP 3A4 and 2C19 [431]. One clinical study in healthy subjects that investigated the effects of rifampicin, ketoconazole, and omeprazole on the pharmacokinetics of THC and CBD delivered from Sativex® reported that co-administration of rifampicin with Sativex® is associated with slight decreases in the plasma levels of THC, CBD, and 11-hydroxy-THC, while co-administration of ketoconazole with Sativex® is associated with slight increases in plasma levels of THC, CBD, and significant increases in the plasma levels of the potent psychoactive metabolite 11-hydroxy-THC (i.e. more than three-fold) [470]. Co-administration of Sativex® with ketoconazole was also associated with an increase in the frequency of treatment-emergent adverse events primarily involving the nervous system. While no serious adverse effects were noted, there were increases in the incidence of somnolence, dizziness, euphoric mood, lethargy, anxiety, dysgeusia, and headache. No significant effects on plasma levels of THC, CBD or 11-hydroxy-THC were noted with omeprazole.

Cannabinoid–mediated regulation of drug metabolism and drug transport

While THC, CBD, and CBN are known to inhibit CYP isozymes such as CYP 1A1, 1A2, 1B1 and 2A6 [74, 468], smoke from cannabis may also induce CYP 1A1 and 1A2 to an extent similar to that seen with tobacco smoke with added effects when used in combination, most likely through the effects of polyaromatic hydrocarbons from burning plant material on the aromatic hydrocarbon receptor [1390]. Induction of CYP 1A1/1A2 may result in decreased plasma levels of chlorpromazine and theophylline [473, 1390-1393]. Despite the potential for CYP induction from cannabis smoke, additional data from *in vitro* experiments suggests that Δ^9-THC also has the potential to inhibit CYP isozymes 3A4, 3A5, 2C9, and 2C19, while CBD also has the potential to inhibit CYP 2C19, 3A4, and 3A5 [74, 431]. THC, CBD or CBN as well as cannabis containing these cannabinoids may therefore increase the bioavailability of drugs metabolized by these enzymes. Such drugs include amitryptiline, phenacetin, phenytoin, theophylline, granisetron, dacarbazine, and flutamide [74].

There is also some evidence to suggest a potential interaction between CBD and phenytoin: both substances have closely related spatial conformation features, both act as anti-convulsants, CBD inhibits CYP 2C19, 3A4, 1A2, and 2A6 which metabolize phenytoin or phenytoin metabolites, and in addition, evidence from pre-clinical studies suggest CBD enhances the anticonvulsant effects of phenytoin [468, 745, 1394]. As such, patients taking CBD and anti-convulsants such as phenytoin should be monitored for increased blood levels of phenytoin, and doses of phenytoin should be adjusted accordingly to avoid the potential for excess blood levels of phenytoin and a phenytoin overdose.

A clinical study in children with refractory epilepsy and taking CBD (Epidiolex®) (5 mg/kg/day up to a maximum of 25 mg/kg/day) and clobazam (mean daily dose = 1 mg/kg/day, range: 0.18 – 2.24 mg/kg/day) for seizure control reported a CBD-mediated elevation in plasma levels of clobazam and its metabolite, n-desmethylclobazam [236]. Clobazam and n-desmethylclobazam are metabolized by CYP3A4 and 2C19 to varying degrees and CBD has been shown to inhibit both of these CYPs. Mean increase in clobazam levels was 60% at four weeks (but not deemed statistically significant) following treatment and a mean increase in n-desmethylclobazam levels of 500% at four weeks (deemed statistically significant). Nine out of 13 children showed a > 50% decrease in seizures, and side effects (increased seizure frequency, ataxia, restless sleep, tremor, drowsiness, irritability, loss of appetite, and urinary retention) were managed by a dose reduction in clobazam. The authors of the study recommend monitoring of clobazam and n-desmethylclobazam levels in the clinical care of patients concomitantly taking clobazam and CBD (Epidiolex®).

In addition, 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* [72]. CBD may also potentially inhibit UDP-glucuronosyltransferases 1A9 and 2B7 and CBN may potentially inhibit UDP-glucuronosyltransferase 1A9 [468]. This suggests a potential additional role for these cannabinoids in affecting the therapeutic drug efficacy and toxicity of co-administered drugs [72].

In light of the evidence, clinicians should therefore be aware of 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 be at risk of experiencing adverse effects if co-consuming cannabis/cannabinoids [471, 473, 474, 834, 1395].

In one study, subjects reported an increase in the intensity and duration of the "high" when oxycodone was combined with inhalation of vapourized THC-predominant cannabis; this effect was not observed when morphine was combined with inhalation of vapourized cannabis [280]. Furthermore, in that study, inhalation of vapourized THC-predominant cannabis was associated with a statistically significant decrease in the 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. There were no changes in the AUC for morphine metabolites, or in the ratio of morphine metabolites to parent morphine. In contrast to the effects seen with morphine sulfate, inhalation of vapourized THC-predominant cannabis was not associated with any changes in oxycodone pharmacokinetics.

A double-blind, placebo-controlled, cross-over clinical study was carried out to determine the safety and pharmacokinetics of CBD co-administered with intravenous fentanyl [1396]. Seventeen healthy volunteers were recruited into the study and administered placebo, 400 or 800 mg oral CBD (10 – 15 mg/kg) followed by a single dose of either 0.5 or 1.0 µg/kg dose of intravenous fentanyl. No significant pharmacokinetic changes were noted with CBD and opioid co-administration at the doses tested. In addition, Systematic Assessment of Treatment Emergent Events (SAFTEE) data were similar between treatment groups without any respiratory depression or cardiovascular complications during any test session. Minor adverse events reported by subjects during and immediately after study sessions included: dizziness/drowsiness, itching or rash, headache, abdominal discomfort, nausea/vomiting, and diarrhea.

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 [465].

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 [58, 59, 195, 216, 222, 280, 281, 287, 386, 433, 598, 598, 599, 612, 822, 834], cancer-related pain [138, 283, 284], fibromyalgia [184, 386, 596, 597], pain and spasticity associated with MS [278, 387, 432, 610, 686, 835], and symptoms associated with HD or PD [245, 254].

Examples of commonly-used medications seen in clinical trials of cannabis or prescription cannabinoid medications (e.g. dronabinol, nabilone and nabiximols) include NSAIDs (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, anxiety, headache, but also dry mouth, hypotension, tachycardia, throat irritation (with smoking) and gastrointestinal disorders (nausea)).

One study has reported that 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 itself been associated with adverse cardiovascular events [1397].

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 [1398, 1399] depending on among other things, the sensitivities of the tests used, frequency of cannabis use and timing of testing.

7.0 Adverse effects

Reporting adverse reactions associated with the use of cannabis and cannabis products is important in gathering much needed information about the potential harms of cannabis and cannabis products for medical purposes. When reporting adverse reactions, please provide as much complete information as possible including the name of the licensed producer, the product brand name, the strain name, and the lot number of the product used in addition to all other information available for input in the adverse reaction reporting form. Providing Health Canada with as much complete information as possible about the adverse reaction will help Health Canada with any follow-ups or actions that may be required.

Healthcare practitioners and consumers are invited and encouraged to submit reports of all adverse effects associated with cannabis for medical purposes to Canada Vigilance in the following ways:

Report online, call toll-free at 1-866-234-2345, complete a Canada Vigilance Reporting Form and fax toll-free to 1-866-678-6789, or Mail to:

Canada Vigilance Program
Health Canada
Postal Locator 0701D
Ottawa, Ontario K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site.

There is generally far more information available in the medical literature on the adverse effects associated with non-medical 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 non-medical users. 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 most 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 [1400]. The most frequently cited adverse events associated with the use of prescription cannabinoid medications (e.g. dronabinol, nabilone, nabiximols) were nervous system disorders, psychiatric disorders, GI disorders, and vascular and cardiac disorders.

A multi-centre, prospective, cohort safety study of patients using cannabis as part of their pain management regimen for chronic non-cancer pain reported that cannabis use was not associated with an increase in the frequency of serious adverse events compared to controls, but was associated with an increase in the frequency of non-serious adverse events [216]. In this study, 216 patients with chronic non-cancer pain (nociceptive, neuropathic, both) using cannabis and 215 control patients with chronic pain but no cannabis use were followed for a period of one year and evaluated for frequency and type of adverse effects associated with the use of a standardized herbal cannabis product (CanniMed 12.5% THC, <0.5% CBD). A significant proportion of study subjects were taking opioids, anti-depressants or anti-convulsants. Almost one third of study subjects consumed it exclusively by smoking, 44% by smoking and oral ingestion, 14% by vapourizing, smoking or ingesting cannabis orally, and slightly less than 4% reported only smoking or vapourizing. The most common adverse event categories in the cannabis-treatment group were nervous system (20%), GI (13.4%), and respiratory disorders (12.6%) and the rate of nervous system disorders, respiratory disorders, infections, and psychiatric disorders was significantly higher in the cannabis group than in the control group. Furthermore, mild (51%) and moderate (48%) events were more common than severe ones (10%) in the cannabis-treatment group. Somnolence (0.6%), amnesia (0.5%), cough (0.5%), nausea (0.5%), dizziness (0.4%), euphoric mood (0.4%), hyperhidrosis (0.2%), and paranoia (0.2%) were assessed as being “certainly/very likely” related to treatment with cannabis. Interestingly, increasing the daily dose of cannabis was not associated with a higher risk of serious or non-serious adverse events, although the total daily amount of cannabis allowed was set at 5 g per day (the median daily cannabis dose was 2.5 g per day).

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 [145, 1401-1404] (and also see **Section 6.2**).

7.1 Carcinogenesis and mutagenesis

- ***Evidence from pre-clinical studies suggests cannabis smoke contains many of the same carcinogens and mutagens as tobacco smoke and that cannabis smoke is as mutagenic and cytotoxic, if not more so, than tobacco smoke.***
- ***However, limited and conflicting evidence from epidemiological studies has thus far been unable to find a robust and consistent association between cannabis use and various types of cancer, with the possible exception of a link between cannabis use and testicular cancer (i.e testicular germ cell tumours).***

Pre-clinical studies

Qualitatively, cannabis smoke condensates have been shown to contain many of the same chemicals as tobacco smoke [84]. Furthermore, a number of *in vitro* studies have provided strong evidence that smoke from burning cannabis is carcinogenic (reviewed in [140]). The cytotoxic and mutagenic potential of cannabis smoke condensates were compared to their tobacco counterparts and 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 [82]. In addition, for either cannabis or tobacco smoke, the particulate phase was substantially more cytotoxic than the gas phase. A follow-up global toxicogenomic analysis comparing tobacco and cannabis smoke condensates *in vitro* reported that tobacco smoke condensate exposure was associated with expression of genes involved in xenobiotic metabolism, oxidative stress, inflammation, and DNA damage response [1405]. Furthermore, these same pathways and functions were also significantly affected following exposure to cannabis smoke condensates suggesting that cannabis smoke condensates affect many of the same molecular processes and functions as tobacco smoke condensates, although some notable differences between cannabis and tobacco smoke condensates with regard to affected molecular pathways were noted [1405]. Taken together, these studies suggest that cannabis smoke cannot be deemed "safer" than tobacco smoke. However, despite some persuasive *in vitro* data, the epidemiological evidence for a link between cannabis smoking and cancer remains mainly inconclusive because of conflicting results from a limited number of studies. Below is a summary of the evidence on cannabis use and cancer.

Epidemiological 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 [358]. 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 (OR = 2.6; CI = 1.1 – 6.6), with a strong dose-response pattern compared to non-smoking controls [359]. 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 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 [360].

However, a much smaller case-control study 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% CI = 2 – 15%) for each "joint-year" (defined as the smoking of one joint per day for one year), after adjusting for cigarette smoking [361].

A population-based, longitudinal cohort study examined over 49 000 men aged 18 to 20 years old for cannabis use and other relevant health variables during military conscription in Sweden [1406]. Participants were tracked over a 40-year period for incident lung cancer outcomes in nationwide linked medical registries. Analysis found that "heavy" cannabis smoking (but not "ever" use) was significantly associated with more than a two-fold risk (hazard ratio = 2.12, 95% CI = 1.08 – 4.14) of developing lung cancer over the 40-year follow-up period even after statistical adjustment for baseline tobacco use, alcohol use, respiratory conditions and socio-economic status. However, the vast majority of individuals reporting cannabis use also reported tobacco use and there was no clear evidence of a dose-response relationship between frequency of cannabis use and lung cancer outcomes. In addition, the study did not include a detailed assessment of use patterns of cannabis and tobacco preceding the baseline conscription process and it also did not have any information about tobacco and cannabis use after conscription.

A recent meta-analysis of 4 cohort studies and 30 case-control studies (11 studies on upper aerodigestive cancers, 6 studies on lung cancer, 3 studies on testicular germ cell tumours, 6 studies on childhood cancers, 1 study on all cancers, 1 study on anal cancer, 1 study on penile cancer, 2 studies on non-Hodgkin's lymphoma, 1 study on malignant primary glioma, 1 study on bladder cancer, and 1 study on Kaposi's sarcoma) examined the correlation between cannabis use and risk of various cancers [1407]. The meta-analysis concluded that for head and neck cancer, the evidence was inconsistent but may be consistent with no association or with opposite directions of association depending on the subgroups of populations. For lung cancer, while the authors state that it was generally difficult to rule out residual confounding by tobacco use, they suggest that overall the studies available to date suggest no association with cannabis use though the authors are careful to point out that affirming no association is inherently difficult. In light of the multiple lines of evidence that suggest that smoking cannabis may be a risk factor for the development of cancer (e.g. presence of significant amounts of carcinogens in cannabis smoke, increased risks associated with cannabis-specific smoking topology, and pre-clinical and clinical evidence of pre-cancerous lesions) the lack of a clear association with cannabis use raises a number of interesting questions on the reasons behind the lack of an association including the potential anti-tumorigenic role of cannabinoids. Lastly, the meta-analysis concluded that the three case-control studies of testicular cancer reported similar findings with an increased risk observed for modest frequency and duration of use, while for cancers such as bladder cancer and childhood cancers the authors opine that there is insufficient data to make any firm conclusions on an association with cannabis use.

Despite the conflicting evidence surrounding the carcinogenic potential of cannabis smoke in humans, it is advisable to limit (or eliminate) 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 serious 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, and tar, as well as a more efficient extraction of Δ^9-THC from the cannabis material [402, 411-414]. Taken together, these studies support that, owing to safety considerations, smoking should be avoided as a preferred route of cannabinoid administration and other modes of administration such as oral, oro-mucosal, vapourization or rectal administration should preferably be considered as these may be, in some respects, less harmful than smoking.

7.2 Respiratory tract

- ***Evidence from pre-clinical studies suggests that cannabis smoke contains many of the same respiratory irritants and toxins as tobacco smoke, and even greater quantities of some such substances.***
- ***Case studies suggest that cannabis smoking is associated with a variety of histopathological changes in respiratory tissues, a variety of respiratory symptoms similar to those seen in tobacco smokers, and changes in certain lung functions with frequent, long-term use.***
- ***The association between chronic heavy cannabis smoking (without tobacco) and chronic obstructive pulmonary disease, is unclear, but if there is one, is possibly small.***

A review of the effects of regular cannabis smoking on the respiratory tract reported an increase in the prevalence of chronic cough and sputum production, wheezing, and shortness of breath and an increased incidence of acute bronchitic episodes or clinic visits for acute respiratory illness [1408]. However, at present, no conclusive positive associations can be drawn between cannabis smoking and incidence of lung or upper airway cancer, despite the presence of pro-carcinogenic compounds in cannabis smoke [1407, 1408] (and see **Section 7.1**). There have also been isolated case reports of pulmonary aspergillosis in immunocompromised patients smoking cannabis, reports of pulmonary tuberculosis in those smoking cannabis through contaminated water pipes, as well as reports of pneumothorax, pneumomediastinum, and lung bullae in heavy cannabis smokers [1408]. Overall, the synthesis of the evidence suggests that the risks of pulmonary complications of regular cannabis smoking appear to be relatively smaller and lower than those associated with tobacco smoking, though this does not mean that cannabis smoking can be considered "safe" or safer than tobacco smoking. Furthermore, any risks associated with smoking cannabis should be weighed against any potential therapeutic effects of cannabis.

Below is a select summary of the literature on the effects of cannabis smoking on the respiratory tract.

Differences in the smoking techniques used by cannabis vs. tobacco smokers (i.e. larger puffs, deeper inhalation, and longer breath holding) are reported to result in three- or four-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 [1408, 1409].

A systematic comparison of the mainstream smoke composition from cannabis (12.5% THC, < 0.5% CBD) 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 [84]. The "standard" condition reflects typical tobacco cigarette smoking conditions, whereas the "extreme" condition approaches that typically seen in cannabis smoking. 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 histopathological changes including basal cell hyperplasia, stratification, goblet cell hyperplasia, cell disorganization, inflammation, basement membrane thickening, and squamous cell metaplasia [363, 1408]. 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 some changes in pulmonary function, especially in heavy cannabis smokers, including reduction of FEV_1, an increase in airway resistance, and a decrease in airway conductance [367-369]. Heavy chronic cannabis smokers presented with symptoms of bronchitis, including wheezing, production of phlegm and chronic cough [145, 1410]. All changes were most evident in heavy chronic users, defined as those who smoked more than three joints per day for 25 years [358, 1411], 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 to 10 cigarettes/day [1412].

While the potential risk of developing chronic obstructive respiratory disease, with long-term cannabis use and/or dependence, has been claimed to be potentially as great as among tobacco users [1412], a 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 (i.e. the **C**oronary **A**rtery **R**isk **D**evelopment **I**n Young **A**dults study, **CARDIA**) suggested a more complex picture. The study found a non-linear association between cannabis smoking and pulmonary function [370]. By comparison, tobacco smoking (current and lifetime) was linearly associated with lower FEV_1 and FVC. Low levels of cumulative cannabis smoking were not associated with adverse effects on pulmonary function. Instead, at this level, cannabis smoking was associated with an increase in the FEV_1 and FVC values. 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 cannabis smoking (> ~30 joint-years or > ~25 smoking episodes per month) was associated with an accelerated decline in pulmonary function (FEV_1 but not FVC).

A cross-sectional observational study of 500 individuals in a general practice population (248 tobacco-only smoking individuals, 252 cannabis and tobacco smoking individuals) reported that individuals reporting smoking cannabis (and tobacco) self-reported more respiratory symptoms (i.e. expectoration of sputum, wheeze) than individuals only reporting smoking tobacco [371]. Most study participants who reported smoking cannabis said they smoked cannabis resin (in a joint along with tobacco), with a smaller group reporting smoking herbal cannabis. Each additional joint-year of cannabis use was associated with a small 0.3% increase (95% CI = 0.0 to 0.5) in prevalence of chronic obstructive pulmonary disease. 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, especially chronic obstructive pulmonary disease.

Smoking cannabis may also increase the risk of developing respiratory infections in chronic users [1413] through exposure to infectious organisms such as fungi and molds which can be found in the plant material [1414], or alternatively by decreasing natural host defenses [1415]. However, further epidemiological research is also required to establish a causal relationship between cannabis smoking and respiratory infections.

Vapourization of dried cannabis may be considered an alternative to smoking, although research is required to determine if there are any adverse effects associated with long-term vapourization on lung health/function. In addition, the picture has further evolved with the emergence of cannabis electronic cigarettes ("e-cigs" or "e-joints") containing THC and/or CBD in various solvent carriers such as propylene glycol, glycerol or both [1416-1418]. Despite being frequently advertised by manufacturers as a healthier alternative to smoking, there are many uncertainties about the impact of e-cigarettes on health and indoor air quality [1419]. Studies have reported that the aerosols generated from e-cigarettes can contain carcinogens such as formaldehyde, acetaldehyde and acrolein, especially when high voltage devices/settings are used, although even at normal operating settings the levels of formaldehyde, for example, may be elevated despite the absence of the so-called "dry hit" or "dry puff" characterized by an unpleasant taste that more experienced users can detect [1420]. Various design and operating parameters have significant effects on emission levels of toxic compounds, including the choice of vapourizer and the battery power output, both of which determine the coil and vapour temperatures [1421]. Emissions are believed to be caused by the thermal degradation of propylene glycol and/or glycerol [1422, 1423] with the quantity of formaldehyde and other carbonyls increasing with increasing power [1422-1424], and device temperature [1425]. Therefore, overly high temperatures and a prolonged contact of the heating coil with the e-liquid must be avoided to prevent the formation of toxic pyrolytic by-products, even though lower settings may also yield some of these toxic by-products [1416]. The extent of toxicant exposure that might occur during normal use of e-cigarettes is currently unclear, although one urinary biomarker study suggested that exposure to other reactive carbonyls (e.g. acrolein, crotonaldehyde) was significantly lower among vapers than among cigarette smokers [1426]. Aside from inhaling the mentioned carcinogenic by-products, active vapers may also be inhaling relatively high concentrations of propylene glycol, glycerol, and aerosol particulates [1419]. Lastly, there have been a few case reports of exogenous lipoid pneumonia, eosinophilic pneumonitis, and subacute bronchial toxicity associated with vaping glycerol-based e-liquids [1427-1429]. For additional information on vapourization please consult **Sections 1.1.1, 1.1.2, 2.2.1.2, 3.4, 4.7.2.2, 4.7.2.3**, and **Table 4**.

7.3 Immune system

- ***Pre-clinical studies suggest certain cannabinoids have a variety of complex effects on immune system function (pro-/anti-inflammatory, stimulatory/inhibitory).***
- ***The limited clinical and observational studies of the effects of cannabis on immune cell counts and effect on HIV viral load are mixed, as is the evidence around frequent cannabis use (i.e. daily/CUD) and adherence to ART.***
- ***Limited but increasing evidence from case studies also suggests cannabis use is associated with allergic/hypersensitivity-type reactions.***

Pre-clinical studies

Evidence from *in vivo* and *in vitro* studies suggests complex and apparently dichotomous roles for the ECS on immune system function [26]. 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 and 100 : 1, depending on the immune cell type in question [26, 27]. In addition, CB_2 receptor expression is most abundant in B-cells, followed by natural killer cells, monocytes, neutrophils and lastly, T-cells [1430]. Second, immune cells also have the ability to synthesize, secrete, transport and catabolize endocannabinoids [26]. 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 [26]. 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 ECS by upregulating the expression of both CB_1 and CB_2 receptor mRNA and protein levels [27]. Thus, there appears to be some level of cross-talk between the endocannabinoid and immune systems. Fifth, as is the case for some of its other effects, 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 [392]. 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 [392, 1431, 1432]. Cannabinoids target various cellular signaling and transcriptional pathways resulting, in some instances, 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) [27, 392]. CBD also appears to induce a shift in Th1/Th2 immunobalance [1431].

While under certain circumstances, cannabinoids appear to have broad anti-inflammatory and immunosuppressive effects, which could be of benefit in pathological conditions having inflammatory characteristics, such effects may become problematic in the context of essential defensive responses to infections [26]. For example, *in vitro* as well as *in vivo* experiments suggest cannabinoids (i.e. THC) have an impact on virus-host cell interactions [1433]. Cannabinoid treatment (i.e. THC) has been associated with *increased* viral replication of the herpes simplex virus-2, HIV-1, Kaposi's sarcoma-associated virus, influenza, and vesicular stomatitis virus, or has been associated with *increases* in surrogate measures of infection in these experimental models suggesting that at least some cannabinoids (THC) could have a detrimental effect with regard to viral infections [1430, 1434-1441]. Another study has also shown that chronic THC exposure decreased the efficacy of the memory immune response to *Candida albicans* infection in a mouse model [1442]. However, in male rhesus macaques, chronic administration of THC (0.32 mg/kg b.i.d.) is associated with decreased early mortality from SIV infection, attenuation of plasma and CSF and gut viral load, decreased GI inflammatory responses, decreased viral replication, and modest retention of body mass [1443-1445]. However, similar protective effects were not observed in female macaques [1446] suggesting a sex-dependent effect.

Thus, the available pre-clinical evidence suggests that cannabinoids may systematically influence viral infection through a number of mechanisms that include the regulation of host immunity and inflammatory responses, cell metabolism, the ability to enter the host cells, integrate into the host genome, replicate, and be released, as well as novel epigenomic and miRNA regulatory mechanisms [1434]. Furthermore, 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, and also by differences between species, the experimental protocols and outcome measures used, and in addition for clinical studies (see below), the health status/medical condition of the human subjects [392].

Clinical studies

The effects of smoked cannabis/THC on the human immune system have been studied, albeit only to a limited degree and the evidence is mixed. While *in vitro* studies with human immune cells suggest that THC has immunosuppressive properties[1447-1453], data from clinical studies of smoked cannabis and psychoactive cannabinoids (oral THC, oral THC/CBD) do not appear to show an increased risk of infections or infestations in patients using smoked cannabis/cannabinoids [216, 1400].

Cannabis and immune cell count

A major concern with immunocompromised individuals such as HIV-positive cannabis smokers, or patients smoking and 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 [642]. A group of studies has partially addressed the former concern.

In one study, HIV-positive patients on stable ART 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 [1454]. 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 [1455]. Cannabis use was also not associated with an increased rate of progression to AIDS in HIV-infected individuals [1456]. In another study, smoking cannabis was associated with lower plasma concentrations of the protease inhibitors indinavir and nelfinavir; whereas dronabinol or placebo had no effect [471]. However, the decreased plasma levels of protease inhibitors were not associated with an elevated viral load, or changes in CD4+ or CD8+ cell counts [655]. Furthermore, a retrospective, longitudinal, observational cohort study among ART-naïve illicit drug users reported that at least daily cannabis use was associated with *lower* plasma HIV-1 RNA viral load in the first year following seroconversion [1457]. In another study, HIV positive cannabis users (light or moderate-to-heavy use) showed higher plasma CD4 counts and lower viral load than HIV positive non-cannabis users; the ART status of the subjects was not known [1458]. On the other hand, an observational study of 157 men who have sex with men found that cannabis use during sexual intercourse was significantly associated with higher likelihood of elevated seminal plasma HIV RNA viral load despite successful combined ART [1459]. In humans, smoking cannabis was also associated with poorer outcome in patients with chronic hepatitis C [1402, 1460].

Cannabis and anti-retroviral treatment adherence

One cross-sectional study examined the association between cannabis use status and adherence to ART as well as the association between cannabis use status, HIV symptoms, and side effects associated with ART among a sample of HIV-positive individuals [1461]. The study reported that those subjects who had a CUD had a significantly lower adherence to treatment than those who reported using cannabis once or more per week, but less than daily or not at all. Those who had a CUD also had a higher viral load than those who used cannabis less than daily but at least once per week, as did those who did not use at all; absolute CD4 count was not significantly different between groups. Furthermore, those subjects with a CUD 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. One limitation to this study was its cross-sectional nature, precluding the ability to establish a cause-and-effect relationship.

On the other hand, a long-term, observational, prospective cohort survey study (the **A**IDS **C**are **C**ohort to evaluate **E**xposure to **S**urvival **S**ervices, **ACCESS**) that examined the relationship between high-intensity cannabis use and adherence to ART among 523 HIV-positive illicit drug users reported that at least daily or more often than daily cannabis use was not associated with adherence to ART [1462].

CBD and graft-versus-host disease

A phase II, non-randomized, uncontrolled, unblinded clinical study of the effects of CBD on the prevention of graft-versus-host disease (GVHD) after allogeneic hematopoietic cell transplantation reported that oral administration of CBD (300 mg/day) beginning seven days before transplantation and continuing for a period of 30 days post-transplantation was associated with a reduction in the incidence of acute GVHD when combined with standard GVHD prophylaxis (i.e. cyclosporine and methotrexate) [1463]. Furthermore, no Grade 3 or 4 toxicities were attributed to CBD treatment. Forty-eight adult patients were enrolled in this clinical trial, with 38 patients having acute leukemia or myelodysplastic syndrome and 35 patients given myeoablative conditioning. Limitations of the study included single-arm design, and retrospective comparison with historical control subjects. Nevetherless, the findings from this study suggest CBD may have significant immunosuppressive properties. Further research is needed.

Hypersensitivity/allergic reactions
There are increasing reports of hypersensitivity/allergic reactions to cannabis [365, 393, 394, 1353, 1354]. Clinical symptoms of such reactions include sore throat, nasal congestion, rhinitis, conjunctivitis, pharyngitis, food allergy, eczema, contact urticaria, anaphylaxis, wheezing, dyspnea, palpebral angioedema and lacrimation [365, 393, 1353]. In chronic and high dose users more severe manifestations of bronchitis and asthma with reduced vital capacity have been noted [1353]. Furthermore, cannabis allergy has also been associated with cross-allergies to other plants such as wheat, tobacco, latex, nuts, and certain fruits and vegetables (e.g. tomato, cherry, tangerine, banana, citrus, grapefruit, pepper, fig, peach peel, apple, hops, grapes) [365, 393, 394].

7.4 Reproductive and endocrine systems

- ***Pre-clinical evidence suggests certain cannabinoids can have negative effects on a variety of measures of reproductive health. Furthermore, limited evidence from human observational studies with cannabis appears to support evidence from some pre-clinical studies.***
- ***Evidence from human observational studies also suggests a dose- and age-dependent association between cannabis use and testicular germ cell tumours.***
- ***Pre-clinical evidence clearly suggests in utero exposure to certain cannabinoids is associated with a number of short and long-term harms to the developing offspring.***
- ***However, evidence from human observational studies is complex and suggests that while confounding factors may account for associations between heavy cannabis use during pregnancy and adverse neonatal or perinatal effects, heavy cannabis use during pregnancy is associated with reduced neonatal birth weight.***

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—brain structures involved in regulating different reproductive and sexual behaviours and endocrine functions [397]. 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 endocrine effects through the HPA axis either directly by modulating the gonadotropin-releasing hormone or indirectly through other pathways [397, 1464].

CB_1 receptor-mediated modulation of the HPA 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 point to a probable suppression of release [395, 399, 1465, 1466]. In animals, these effects are accompanied by changes in reproductive function and behaviour including anovulation, decreases in plasma testosterone levels, degenerative changes in spermatocytes and spermatids, and potential reduction in copulatory behaviour [1464, 1465]. Aside from the roles of the cannabinoid receptors in the brain, the male and female reproductive systems also contain an ECS, and increasing experimental evidence suggests important roles for this ECS in regulating various reproductive functions such as folliculogenesis, spermatogenesis, ovulation, fertilization, oviductal transport, implantation, trophoblast survival, embryo development, pregnancy, and labour (reviewed in [39, 1376]). Tight regulation of endocannabinoid signaling tone across multiple stages of early pregnancy appears critical for female reproductive success [1376].

Effects of cannabis on human sexual behaviour
There is a relative paucity of data with regard to the effects of cannabis or cannabinoids on human sexual behaviour. One review article has summarized the few available studies on the subject [397]. 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 in relaxation, and a corresponding increase in sexual responsiveness) at low to moderate doses, and potentially opposite responses at higher doses. 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. Results obtained from animal studies appear to mirror some of these findings, although exceptions have been noted. 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), and/or to a loss of inhibitions and an increased state of relaxation. In contrast, a recent cross-sectional epidemiological study among 28 176 women and 22 943 men reported that cannabis use frequency was associated with increased coital frequency in both women and men [398].

Effects on sperm and testicular health

The ECS has been implicated in spermatogenesis and production of testosterone [1467-1471]. Human spermatozoa have been shown to express functional CB_1 and CB_2 receptors [1471]. CB_1 and CB_2 receptors have been identified on the plasma membrane of human spermatozoa and the CB_1 receptor has been further shown to be localized to the plasma membrane of the acrosomal region, although also to the midpiece, and the sperm tail [1471, 1472]. The CB_2 receptor on the other hand has been shown to be localized in the post-acrosomal region, midpiece and sperm tail [1471, 1473, 1474]. *In vitro* studies have reported that activation of the CB_1 receptor by anandamide can negatively affect human sperm motility, capacitation and the acrosome reaction [1471, 1472, 1474, 1475]. Hyper- as well as hypo-activation of the CB_2 receptor in male germ cells has been shown to disrupt the temporal dynamics of the spermatogenic cycle [1476]. A cross-sectional study of 86 men presenting at an infertility clinic reported that seminal plasma anandamide levels were significantly lower in men with asthenozoospermia or oligoasthenoteratozoospermia compared with normozoospermic men [1471]. In addition, levels of spermatozoal CB_1 mRNA were significantly decreased in men with asthenozoospermia or oligoasthenoteratozoospermia compared with normozoospermic men [1471]. These findings suggest an association between lower seminal plasma anandamide level and abnormal sperm motility. Furthermore, taken together, these findings suggest an important role for the ECS in sperm function and male reproduction [1477] and also raise the possibility that exposure to exogenous sources of cannabinoids (e.g. THC from cannabis) may affect sperm function. Cannabinoids are lipophilic and they can accumulate in membranes and testicular/epididymal fat from where they can be released slowly;this can affect spermatozoa and their function [395].

THC

The effects of cannabis and Δ^9-THC on human sperm have been investigated both *in vivo* and *in vitro* [395, 1478-1480]. 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 [1478]. 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 [1480]. Decreased sperm motility was observed in both fractions in response to Δ^9-THC concentrations, mimicking those attained non-medically (0.32 and 4.8 μM), and in the 45% fraction in response to 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 raise the possibility that cannabis (i.e. Δ^9-THC) can impair crucial sperm functions and male fertility, especially in those males already on the borderline of infertility [1480].

CBD

In young male mice, IP administration of CBD at dose levels of 10 or 25 mg/kg (57 mg or 142 mg/70 kg)[i] for 5 consecutive days did not adversely affect sperm morphology [1481]. In another study, female mice were exposed to a single oral dose of 50 mg/kg CBD (284 mg/70 kg)[i] on Day 12 of gestation or within 12 hours of parturition. Males whose mothers had received CBD on Day 1 postpartum had approximately 20% less spermatozoa. The percentage of successful impregnations by males whose mothers had received CBD was reduced compared to control. Testicular weight was also reduced in male mice exposed to CBD on Day 12 of gestation [1482]. In another study, male offspring of female mice who received a single oral dose of 50 mg/kg CBD (284 mg/70 kg)[i] on gestational Day 18, had significantly increased testes and seminal vesicles weights [1483]. Maternal exposure to a single oral dose of 50 mg/kg CBD within 12 hours of parturition resulted in long-term alterations in neuroendocrine function in male and female offspring. In addition, in CBD-exposed males, testes weight was significantly reduced and testicular testosterone concentraton was reduced [1484].

Studies investigating the effects of cannabis consumption on testosterone levels in men have yielded conflicting results [397]. 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, while a more recent study found an increase in testosterone levels [396, 397]. 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 [397].

An epidemiological study examining the association between cannabis use and male reproductive hormones and semen quality among 1 215 healthy young men, 18 – 28 years of age, reported that regular cannabis smoking (> 1 / week) was associated with a 28% reduction (95% CI: -48, -1) in sperm concentration and a 29% reduction (95% CI: -46, -1) in sperm count after adjustment

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[i] Human equivalent doses were calculated based on body surface area: animal doses in mg/kg were divided by 12.3 for mice [1661]

for confounders but was also associated with higher levels of testosterone [396]. Combined use of cannabis more than once per week with other non-medical drugs was associated with a 52% reduction (95% CI: -68, -27) in sperm concentration and 55% reduction in total sperm count (95% CI: -71, -31). The authors also noted higher testosterone levels in male cannabis smokers within the same range as cigarette smokers.

A systematic review and meta-analysis of studies examining cannabis exposure and risk of testicular cancer found that current, chronic and frequent cannabis use was associated with testicular germ cell tumours (TGCT) when compared to never-use of cannabis [362]. Out of 149 records retrieved, only three case-control studies [1485-1487] met the rigorous inclusion criteria for meta-analysis. The meta-analysis was inconclusive with respect to the association between ever-use of cannabis and the development of TGCT (pooled OR = 1.19, CI = 0.72 – 1.95) for ever-use compared to never-use. A similar finding was obtained with former use and TGCT (pooled OR = 1.54, CI = 0.84 – 2.85). In contrast, current use of cannabis increased the odds of development of TGCT by 62% (OR = 1.62, CI = 1.13 – 2.31). Furthermore, frequency of cannabis use was associated with TGCT development, with weekly (or greater) use nearly doubling the odds of TGCT development (OR = 1.92, CI = 1.35 – 2.72). In addition, there was evidence of an association between duration of cannabis use (> = 10 years vs. never-use) and TGCT development (OR = 1.50, CI = 1.08 – 2.09). There was also evidence of an association between cannabis use and non-seminoma development, with current use more than doubling the odds of tumour development (OR = 2.09, CI = 1.29 – 3.37). Those using cannabis on an at least weekly basis had 2.5 times greater odds of tumour development compared to those who never used. Those who had used cannabis for at least 10 years had nearly 2.5 times the odds of non-seminoma development compared to never-use. There was insufficient evidence to conclude a relationship between seminoma tumours and cannabis use. The authors of the study suggest that cannabis use before age 18 may increase the risk of developing non-seminoma TGCT (AOR = 2.80, CI = 1.60 – 5.10) compared to use after age 18 (AOR = 1.30, CI = 0.60 – 3.20).

Effects on foetal development and child/adolescent development

Foetal development

Cannabis is the substance most abused by pregnant women: in the U.S. its prevalence exceeds 10% among pregnant women [1488]. Women self-report using cannabis during pregnancy for its antiemetic properties, especially during the first trimester [1489]. Relatively little is known about the changes in cannabis pharmacokinetics during pregnancy and the maternal-fetal transfer and fetal pharmacokinetics of THC [1384]. THC and its metabolites can be detected in meconium and infant urine (as an indicator of maternal cannabis use). THC readily crosses the placenta but may be actively transported out of the placenta [1384]. Placental concentrations of THC have been reported to average 200 ng/g while the mean THC level in fetal remains was 119 ng/g [1384]. Because the ECS is an evolutionarily conserved signaling network that has been shown to guide critical aspects of brain development [1488] and because THC has been shown to cross into the placenta, this has raised concern that cannabis use during pregnancy, and even during the perinatal period, can have deleterious effects on foetal development and potentially on child, adolescent and adult development [1384].

Pre-clinical studies

In vitro exposure to THC caused dose-dependent inhibition of embryonic development to blastocysts, but even at the highest concentration used (160 nM), there was never a complete arrest of embryonic development. THC was relatively less potent than the other synthetic cannabinoid agonists (CP 55,940, Win 55,212-2, and anandamide); the other cannabinoid agonists only required 0.7 to 14 nM to inhibit embryonic development. The developmental arrest primarily occurred between the four-cell and eight-cell stages [1379].

In vitro, exposure to CBD at concentrations of 6.4 to 160 nM did not significantly alter embryonic development [1379, 1490]. In addition, i*n vitro* exposure to 1 to 25 µM CBD did not affect the viability of stabilized nontumour cell lines (human keratinocytes, rat preadipocytes, and mouse monocyte macrophages). Viability of glial cells was also not affected by the treatment with CBD up to 50 µM [1490].

In utero exposure to THC or cannabinoids in rodents is associated with axonal bundle malformation prenatally; decreased birth weight neonatally; increased rearing and locomotor activity, hyperactivity, learning impairment, vocalization, and impaired synapse formation postnatally; altered open field performance, impaired consolidation of long-term memory and inhibited social interaction and play behaviour during adolescence; and memory impairment, reduced synaptic plasticity, cognitive impairment, altered social behaviour, and an anxiogenic-like profile in adulthood [1381].

A study conducted in pregnant mice using a low dose of THC has been shown to alter the expression level of 35 proteins in the fetal cerebrum [62]. Furthermore this study concretely identified a specific molecular target for THC in the developing CNS whose modifications can directly and permanently impair the wiring of neuronal networks during corticogenesis by enabling formation of ectopic neuronal filopodia and altering axonal morphology. Another *in vitro* study with retinal ganglion cell explants showed that CBD (300 nM) decreased neuronal growth cone size and filopodia number as well as total projection length and induced growth cone collapse and neurite retraction (i.e. chemo-repulsion) through the GPR55 receptor [63].

There is also some emerging evidence from pre-clinical studies that suggests the presence of multigenerational alterations in gene expression and neurotransmission in offspring following *parental* exposure to cannabinoids [1491]. Male and female rats exposed to THC were observed to produce offspring with decreased expression of cannabinoid, dopamine and glutamate receptors, reduced NMDA receptor binding, and enhanced long-term depression in the dorsal striatum [1491, 1492]. Furthermore, THC exposure in mice has been shown to cause genome-wide changes in histone methylation [1491, 1493]. Taken together, these findings raise the possibility that parental exposure to cannabinoids may confer multigenerational and potentially transgenerational effects on offspring gene expression, histone methylation, and neurotransmission [1494].

Clinical studies

Results from human epidemiological studies examining *short-term* neonatal outcomes among women who smoked cannabis during pregnancy are equivocal for some effects; there have been some reports of reduced neonatal birth weight and length [1495-1498] or a slightly increased risk of sudden infant death [1499], but other reports of no effect [1500-1502]. However, a recent systematic review concluded that the most robust effect of cannabis was a reduced birth weight [1362]. On the other hand, there appear to be some long-term effects on the development of children born to mothers who used cannabis heavily during pregnancy. Prenatal cannabis use has been associated with lower scores on language, memory and abstract/visual reasoning domains in children of preschool age [1381, 1503-1505]. In school-aged children, prenatal cannabis exposure was also associated with deficits in attention and presence of impulsivity and hyperactivity [1381, 1506-1508]. Later, in children between 9 and 12 years of age, prenatal cannabis exposure was associated with decreased performance in executive functions (e.g. impaired working memory, inattention, impulsivity and inability to plan) [1509, 1510] with these deficits also appearing in 13 to 16-year olds [1511] and 18- to 22-year olds [1512].

A prospective structural neuroimaging study in young children (ages 6 to 8) (i.e. the "Generation R" study) reported that while prenatal cannabis exposure was not associated with any significant differences in total brain volume, grey matter volume, white matter volume, or ventricular volume, prenatal cannabis use was associated with differences in cortical thickness [1513]. Compared with control subjects not exposed to cannabis, children who had prenatal cannabis exposure had thicker frontal cortices, whereas children prenatally exposed to tobacco exhibited cortical thinning mainly in the frontal and parietal cortices. Increased cortical thickness in cannabis-exposed children raise the possibility of decreased synaptic pruning and altered neurodevelopmental maturation in areas of the brain associated with higher-order cognitive functions.

An epidemiological study of 1 709 randomly selected high school students that investigated the association between parental CUD and risk for CUD among offspring reported higher risks of CUD among offspring with parental histories of CUD, hard drug disorders and antisocial personality disorder [1514]. The hazard ratio for CUD was 1.93 (95% CI = 1.30 – 2.88) among offspring with parental histories of CUD, 1.96 (95% CI = 1.32 – 2.90) among offspring with parental histories of hard drug use disorders, and 1.73 (95% CI = 1.06 – 2.82) for the offspring of parents with antisocial personality disorder. The effect was particularly significant among female offspring with maternal CUD histories.

Evidence suggests that cannabinoids accumulate in the breast milk of mothers who smoke cannabis and are transferred to newborns through breastfeeding [1385, 1515]. Indeed, the THC concentration of breast milk in humans may be up to eight-fold higher than that found in maternal blood [1385, 1488]. In a case-control study [1516], 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.

A recent review on the risks of cannabis use in pregnancy indicated that more women are turning to cannabis for its antiemetic role in the first trimester, which represents the period of greatest risk for the detrimental effects of drugs to the fetus. However, though the evidence for the effects of cannabis on human prenatal development is currently limited, the authors state that the available research supports a cause for concern. The collective evidence highlights that women who used cannabis during pregnancy compared to women who did not use cannabis during pregnancy were more likely to: be anemic, have a lower birth weight infant, and require placements in neonatal intensive care. Other studies show links between fetal cannabis exposure and adverse long-term outcomes during the school years concerning impulse control, visual memory, and attention. The exact mechanisms behind these effects are understudied, but are theorized to result from cannabis' interference with nervous system development. The endocannabinoid system, – first detected around day 16 of human gestation, is thought to play an important role in neural circuitry and brain development by regulating neurogenesis and migration, the outgrowth of axons and dendrites, and axonal path finding [1517].

Effects on adolescent mental health

Adolescence is an important stage of behavioural maturation and brain development marked by significant neuroplasticity that leaves the brain open to influence by external factors such as drug use [551]. Furthermore, the majority of psychiatric disorders first begin to make their appearance during late adolescence/early adulthood, including disorders such as drug abuse, drug dependence/addiction, anxiety, depression, bipolar disorder and schizophrenia/psychosis [1518, 1519]. The broad and abundant expression of the CB_1 receptor in neuronal circuits involved in dependence/addiction and psychiatric disorders suggest the possibility of an association between the ECS and the pathophysiology of these diseases [551]. During adolescence, the levels of the endocannabinoids anandamide and 2-AG fluctuate considerably across various brain regions such as the striatum and the prefrontal cortex, with the levels of 2-AG being reduced from early to late adolescence and the levels of anandamide appearing to continuously increase in the prefrontal cortex during the course of adolescence [551]. Growing evidence also suggests a differential effect of cannabis exposure (THC) on the human brain that varies according to age of exposure with some evidence suggesting the potential for long-lasting effects associated with early, chronic and long duration of use [182, 541, 551, 552]. Also, see **Sections 2.4, 4.9.5** and **7.7.3** for additional information.

7.5 Cardiovascular system

- ***Pre-clinical studies suggest that ultra-low doses of THC may be cardioprotective on experimentally-induced myocardial infarction.***
- ***Evidence from case studies and observational studies suggests that acute and chronic smoking of cannabis is associated with harmful effects on vascular, cardiovascular and cerebrovascular health (e.g. myocardial infarction, strokes, arteritis) especially in middle-aged (and older) users.***
- ***However, a recent systematic review suggests that evidence examining the effects of cannabis on cardiovascular health is inconsistent and insufficient.***

While cannabis is known to cause peripheral vasodilatation, postural hypotension, and characteristic conjunctival reddening after smoking [1520], the most consistent acute physiological effect of smoking cannabis is dose-related tachycardia [144, 346, 352]. Tolerance to the cardiovascular effects (i.e. hypotension and tachycardia) with chronic use has been reported by some but not by others [141, 181, 324, 1521, 1522]. While cannabis-induced tachycardia is not usually considered dangerous for healthy young users, it may be dangerous to those already suffering from cardiac disorders or angina [140, 1523]. Inhalation of cannabis smoke reduces the amount of exercise required to cause an angina attack by 50% [1524], and has been associated with a five-fold increased risk of myocardial infarction in the first hour following smoking [352]. This increased risk 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 [346, 347, 1525].

A review of drug reporting incidences to a French addictovigilance network, a spontaneous reporting system of serious drug abuse and dependence, over a four-year period (2006 to 2010) reported a doubling in the number of cardiovascular cannabis-related reports [1357]. While overall, the number of cardiovascular cannabis-related reports was small (i.e. 5 cases out of 468 cannabis-related reports in 2006 and 11 cases out of 309 cannabis-related reports in 2010), the increase over time was significant and cannabis-related cardiovascular reports represented almost 2% of all incidence reports for all drugs reported to the addictovigilance network. The authors suggest the low numbers likely represent a significant rate of under-reporting, as would be expected both for a typical spontaneous reporting pharmacovigilance program, and for an illicit drug. Patients were mostly men (86%) with an average age of 34 years, and almost half had a history of cardiac or vascular disease and risk factors. The majority of patients (60%) were also concomitant tobacco smokers. Of the 22 cardiac complications reported, 20 were for acute coronary symptoms and 2 were for heart rate disorders. There were also 10 reports for peripheral complications (lower limb or juvenile arteriopathies and Buerger-like diseases) and 3 for cerebral complications (acute cerebral angiopathy, transient cortical blindness, and spasm of cerebral artery). In nine cases, the event led to patient death.

Consistent with the findings of the above review, a number of case-reports of arteritis associated with long-standing, chronic, daily cannabis smoking have also been published [1526-1529]. Case-reports have also suggested an association between chronic, daily cannabis smoking and multi-focal intracranial stenosis [1530] and stroke [356, 357]. One case report described an incidence of hemorrhagic and ischemic stroke following high doses of cannabis (i.e. 4 g per day) [1531]. In this case, the 38 year-old patient had right-sided hemiplegia, motor aphasia, and impairment of consciousness and had a history of frequent alcohol consumption, tobacco smoking (18 pack-years) and cannabis use but no past history of hypertension or any other cardiac, neurological or vascular disease. The authors suggest that altered cerebral autoregulation and regional hypoperfusion may have played a role in the pathogenesis of cannabis-related ischemic stroke and cannabis-induced transient arterial hypertension, and that failure of cerebrovascular autoregulation may have played a role in cannabis-related hemorrhagic stroke.

A general population survey of over 7 500 individuals aged 20 to 64, examining the odds of lifetime stroke/transient ischemic attack (TIA) among participants who had reported smoking cannabis in the past year found that 2.1% had reported having a stroke/TIA [1356]. After adjusting for age cohort, past-year cannabis users had 3.3 times the rate of stroke/TIA (95% CI = 1.8 – 6.3) with this figure diminishing slightly (incident rate ratio (IRR) = 2.3) after adjustment for covariates related to stroke such as tobacco smoking. The elevated risk of stroke/TIA was specific to individuals who used cannabis weekly or more often (IRR = 4.7, 95% CI = 2.1 – 10.7). Furthermore, cases were more common in the older age cohorts with an IRR of 4.9 in the 40 to 44 year-old group vs. the 20 to 24 year-old group and similarly an IRR of 18.1 in the 60 to 64 year-old age group vs. the 20 to 24 year-old age group.

One study has also reported that 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 itself been associated with adverse cardiovascular events [1397].

In contrast with the findings from the above studies with chronic cannabis use (THC), evidence has been obtained in a pre-clinical study that *ultra-low* doses of THC may be cardioprotective [1532]. In this pre-clinical study, the authors report that pre-treatment of mice with an ultra-low dose of THC (0.002 mg/kg) 2 h and 48 h prior to induction of experimental myocardial infarction was associated with partial restoration of cardiac function, an effect that was not observed in mice treated only with a mixture of ethanol, cremophor and saline (1:1:18, respectively), the vehicle used for THC. In addition, pre-treatment with the ultra-low THC dose was associated with a statistically significant reduction in infarct size, significantly lower serum troponin T, reduction in tissue damage, and a decrease in the extent of tissue neutrophil infiltration. The study findings suggest that single application of an ultra-low dose of THC in mice provides a significant protection against an ischemic insult to the heart.

A recent systematic review of 24 studies (22 observational; 2 RCTs) suggests that evidence examining the effect of cannabis on cardiovascular health is inconsistent and insufficient. Based on the limited data, which was rated as poor to moderate quality with high risk of bias, there were no overall significant associations between cannabis use and adverse cardiovascular outcomes related to diabetes, dyslipidemia, acute myocardial infarction, stroke, or cardiovascular and all-cause mortality. Six studies did suggest a metabolic benefit from cannabis use, however, these studies were cross-sectional in nature and do not establish causality. The authors highlighted that data were from 'low risk' cohorts, and that including 'high risk' populations may have revealed different results [1533].

7.6 Gastrointestinal system and liver

- ***Evidence from case reports suggests chronic, heavy (THC-predominant) cannabis use is associated with an increased risk of cannabis hyperemesis syndrome (CHS).***
- ***Limited evidence from observational studies suggests mixed findings between (THC-predominant) cannabis use and risk of liver fibrosis progression associated with hepatitis C infection.***

7.6.1 Hyperemesis

There are an increasing number of case-reports being published regarding the 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 seem to be relieved by compulsive hot water bathing or showering [299-309]. Cannabinoid hyperemesis appears to be triphasic with prodromal, hyperemetic and recovery phases [1534]. The prodomal phase includes nausea and abdominal discomfort, typically worse in the morning. During the hyperemetic phase severe volume depletion can occur accompanied by acute renal failure and electrolytic abnormalities. The recovery phase can last between a few days to months. The pathophysiology of CHS is not well understood [307]. Treatment of patients presenting with this syndrome has been reported to include cessation of cannabis use, rehydration, and psychological counselling [305, 307]. 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 of little value [303, 305, 306, 309]. One 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 [1535].

Limited evidence from a number of case reports has suggested that topical application of capsaicin cream (0.075% to 0.25%) to the abdomen, or any part of the skin (e.g. back or chest), may help alleviate the symptoms associated with CHS within 30 to 45 min of application, with no secondary dermatologic effects, when other known therapeutic measures had failed, with the exception of haloperidol [1534, 1536, 1537].

7.6.2 Liver

A number of studies have strongly implicated the ECS in chronic liver disease [1538-1542]. Studies in patients with chronic hepatitis C have found a significant association between daily cannabis smoking and moderate to severe fibrosis [1460], as well as cannabis smoking being a predictor of fibrosis progression and steatosis severity [1402]. Steatosis is an independent predictor of fibrosis progression and an established factor of poor response to anti-viral therapy [1543]. The authors of the cited studies recommend that patients with ongoing chronic hepatitis C be strongly advised to abstain from daily cannabis use. In contrast, a longitudinal cohort study reported that cannabis smoking was not associated with progression of liver disease, as measured with the AST-to-platelet ratio index (APRI) score, in individuals with HIV-Hepatitis C co-infection [1544]. While smoking cannabis did seem to accelerate progression to a clinical diagnosis of cirrhosis (hazard ratio = 1.33 per 10 joints/week; CI = 1.09 – 1.62), correcting for confounding factors appeared to attenuate this finding. Similarly, cannabis smoking was associated with a slightly increased risk of progression to clinically diagnosed cirrhosis and end-stage liver disease combined (hazard ratio: 1.13, CI = 1.01 – 1.28), but this effect was no longer significant when correcting for confounding factors. Differences in the conclusions between these studies may have been caused by differences in study methodology and also potentially by differences in degree of cannabis exposure (i.e. daily vs. weekly use). 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 ART [376]. 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).

7.7 Central nervous system

The most frequently reported adverse events encountered with (mainly psychoactive) cannabinoids involve the CNS. Commonly reported CNS events in controlled clinical trials with dronabinol (Marinol®, no longer available in Canada) and nabiximols (Sativex®) are intoxication-like reactions including drowsiness, dizziness, and transient impairment of sensory and perceptual functions [227, 431]. A "high" (easy laughing, elation, heightened awareness), which could be unwanted or unpleasant for some 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 [227]. Other adverse events occurring at a rate of > 1% for Marinol® include anxiety/nervousness, confusion, and depersonalization [227]. The rates of dizziness, euphoria, paranoia, somnolence, abnormal thinking ranged from 3 to 10% [227]. The rates of amnesia, ataxia, and hallucinations were > 10% when used as an anti-emetic at higher doses [227]. 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% [1545]. All other intoxication-like effects are reported by less than 5% of users (with the exception of somnolence, 7%) [1545]. Other events reported for Sativex® include disorientation and dissociation. <u>**Many, if not all, of the above-noted CNS effects also occur with (THC-predominant) cannabis.**</u>

7.7.1 Cognition

- ***Evidence from clinical studies suggests acute (THC-predominant) cannabis use is associated with a number of acute cognitive effects.***
- ***Evidence from observational studies suggests chronic cannabis use is associated with some cognitive and behavioural effects that may persist for varying lengths of time beyond the period of acute intoxication depending on a number of factors.***
- ***Limited evidence from human clinical imaging studies suggests THC and CBD may exert opposing effects on neuropsychological/neurophysiological functioning.***
- ***Evidence from mainly cross-sectional human clinical imaging studies suggests heavy, chronic cannabis use is associated with a number of structural changes in grey and white matter in different brain regions.***
- ***Furthermore, early-onset use and use of high-potency, THC-predominant cannabis, has been associated with an increased risk of some brain structural changes and cognitive impairment.***

The *acute effects* of cannabis use on cognition have been well studied [150, 151, 182, 205, 541, 553]. Acute exposure to cannabis (THC) impairs a number of cognitive faculties such as short-term memory, attention, concentration, executive functioning and visuoperception; CBD may protect from some of these impairments [150, 151, 182, 205, 541, 553, 1546-1548].

The *long-term effects* of cannabis exposure on cognition continue to be the subject of some debate. Some studies report a positive association between long-term cannabis consumption and cognitive deficits [150, 151, 1549-1551], or suggest that some cognitive deficits persist after prolonged abstinence (especially when use is initiated during adolescence) [150, 235, 552-554, 1547, 1552]. However, other studies did not find an association between cannabis use and certain long-term cognitive decline [554, 1552, 1553]. Methodological limitations, differences in types of cognitive measures investigated, and differences in length and frequency of exposure, age of onset at which use begins, and duration of abstinence as well as the presence of residual confounding factors and the absence of powerful effects have all contributed to difficulties in assessing the effects of chronic use, and may help explain the discrepancies among studies.

Nonetheless, studies generally suggest that chronic cannabis users may suffer varying degrees of cognitive impairment that have the potential to be long-lasting, especially if use begins earlier on in adolescence (< 16 years of age), is frequent (i.e. daily or near-daily), and persistent (i.e. over the course of years) [147, 182, 205, 541, 552].

In patients with MS and using cannabis, one cross-sectional study showed 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) [233].

In a 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, persistent cannabis use (i.e. CUD) beginning in adolescence was associated with statistically significant global neuropsychological decline across a number of domains of functioning [552]. 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. Correcting for a multitude of confounding factors did not appear to significantly diminish the effect.

However, another study that examined a shorter period of chronic use, more modest use, and in a slightly different age group found that cognitive deficits did not persist beyond the period of intoxication [1553]. In this longitudinal prospective cohort study of 2 235 teenagers (**A**von **L**ongitudinal **S**tudy of **P**arents **A**nd **C**hildren, **ALSPAC**), cannabis users appeared to have lower teenage IQ scores, and poorer educational performance compared to non-users. Furthermore, cannabis users also had higher rates of childhood behavioural problems, childhood depressive symptoms, other substance use (including cigarettes and alcohol) and maternal use of cannabis. However, after adjustment to account for group differences, cannabis use by age 15 did not predict either lower IQ scores at age 15 or poorer educational performance at age 16. The authors suggested that cannabis use at the modest levels used in this sample of teenagers was not by itself causally related to cognitive impairment but acknowledged that the short period of use (1 – 2 years), modest levels of use (≤ 1 week or less) and other factors does not rule out that chronic, frequent, and persistent cannabis use may have adverse effects on cognitive function.

A report that examined the associations between cannabis use and changes in intellectual performance in two longitudinal studies of adolescent twins discordant for cannabis use (n=789 and n=2 277) reported that those twins that had used cannabis had lower test scores compared to non-users and showed a significant decline in crystallized intelligence (i.e. verbal ability, general knowledge) between pre-adolescence and late adolescence [1554]. However, the report failed to find a dose-response relationship between frequency of use and change in IQ and cannabis-using twins did not show significantly greater IQ decline compared to their abstinent siblings. The limitations of this study included methodological challenges leading to an inability to properly measure a dose-response effect.

A recent longitudinal study that examined the adverse effects of cannabis on adolescent brain development reported that repeated heavy exposure to cannabis during adolescence could have a detrimental effect on resting functional connectivity, intelligence, and cognitive function [1555]. Compared to healthy controls, individuals with a diagnosis of CUD showed a decrease in functional connectivity in specific brain regions (i.e. the caudal anterior cingulate and dorsolateral and orbitofrontal cortices) over an 18-month study period. Greater cannabis use over the period between baseline and follow-up predicted low full-scale IQ and predicted lower cognitive function consistent with findings by Meier et al. (2012) [552].

Data from structural and functional imaging studies

The ability of cannabis to affect a variety of cognitive processes both after acute and chronic exposure has inevitably raised questions regarding the structural and functional domains in the brain affected by short and long-term cannabis exposure. Two systematic reviews have been published looking at the acute and chronic effects of cannabis exposure on brain structure and function [1556, 1557]. In general, the findings from studies examining the effects of cannabis exposure on brain structure and function are mixed, mainly owing to the cross-sectional nature of the studies, the lack of consistent and extensive control for confounding variables and small sample sizes [1558]. Findings from a number of such studies are summarized below.

Neurophysiological effects

In the first systematic review of 45 human and animal studies that examined the effects of acute exposure of cannabis on the brain, THC and CBD were found to exert opposing *neurophysiological* effects with the general exception of memory/verbal learning where CBD had no effect [1556]. Acute administration of THC was consistently associated with increases in cerebral blood flow mainly in the prefrontal, insular, cerebellar, and anterior cingulate regions that are known to be enriched in CB_1 receptors and which are responsible for directing a number of cognitive functions as well as playing important roles in the neurobiology of addiction. Subjective levels of intoxication, "feeling high", anxiety, altered time perception, depersonalization, dissociative experiences, and measures of confusion were correlated with increased global cerebral blood flow. Other brain areas where changes in cerebral blood flow were observed in response to THC administration included the basal ganglia, hippocampus/amygdala, thalamus, and all cerebral cortices. Abnormal brain activity has been observed following THC administration during the performance of tasks associated with memory, affective processing, attention, motor function, reward, as well as response inhibition, salience, and sensory processing. CBD appeared to modulate resting brain activity mainly in the limbic and paralimbic cortices, areas implicated in the pathophysiology of anxiety.

Structural effects

In the second systematic review of 43 studies, the findings suggest the existence of *structural* brain abnormalities (mainly in areas of the brain rich in CB_1 receptors) and altered neural activity during resting state and under several different types of cognitive paradigms. In adolescents, the findings suggested structural and functional *alterations* that may appear soon after starting drug use and that could be related to gender [1557]. In terms of *structural* abnormalities, the findings from available studies are heterogeneous with studies reporting either increases or decreases in gray matter volumes, however, the most consistently reported alterations were reduced hippocampal volume (reported to persist at least for several months after last use and associated with amount of cannabis used), as well as reduced amygdala, cerebellum and frontal cortex volume. Diffusion tensor imaging studies have found differences in white matter thickness in the corpus callosum as well as the frontal white matter fibre tract (increases or decreases) which according to the authors suggests that chronic cannabis exposure may alter white matter structural integrity either by affecting demyelination, causing axonal damage, or indirectly through delaying normal brain development. Functional imaging studies comparing *activation* in both adult and adolescent chronic cannabis users with healthy controls during the performance of different cognitive tasks suggest that chronic cannabis users use similar brain areas compared to healthy controls but demonstrate an altered pattern of brain activity. Despite this altered pattern of brain activity, the level of performance of the cannabis users on the cognitive tasks was generally within what the authors considered a normal range of test performance suggesting that the brains of chronic cannabis users engage in neuroadaptive behaviours, by, for example, recruiting other brain areas for tasks to maintain normal cognitive performance. However, while performance may not have been significantly altered in an artificial laboratory setting, the impact of these subtle brain alterations on real-life social and occupational tasks, especially in cognitively complex and demanding contexts, may be different. Limitations of this review include differences between the studies included in the review including methodological differences, socio-demographic differences and differences in gender, age of onset, lifetime use, and abstinence period before the acquisition of imaging data.

More recently, a retrospective study that examined brain morphology in a sample of adult and adolescent daily cannabis users and non-users reported that daily cannabis use was not associated with notable changes in gray matter volume or shape in a variety of brain areas including the nucleus accumbens, amygdala, hippocampus, and cerebellum [1559]. Importantly, this study corrected for a number of confounding factors such as alcohol use and tobacco use that were not always corrected for in other studies. However, significant limitations of the study included a lack of information about the age of onset, history, and duration of exposure to cannabis (i.e. adult use was measured only over past two-month period and adolescent use was measured only over past three-month period), information about the potency or composition of the cannabis used, or socio-economic status. Other limitations of this study included its cross-sectional nature.

A study that investigated the association between cannabis potency, as well as frequency and age of first use, on the microstructural organization of the corpus callosum using diffusion tensory imaging tractography reported that frequent use of high-potency cannabis was associated with disturbed callosal microstructural organization in individuals with and without psychosis [1560]. In this study, 56 individuals with a first-episode of psychosis (of which 37 were cannabis users) and 43 individuals without psychosis (of which 22 were cannabis users) were studied for evidence of structural differences in the corpus callosum, the largest white matter tract in the brain and containing a high abundance of CB_1 receptors. High-potency cannabis users (patients and individuals without psychosis) showed significantly higher mean diffusivity in the corpus callosum (i.e. lower white matter tract density) than both low-potency users and never users. There was also a significant association between the frequency of use on total corpus callosum mean diffusivity with daily users having significantly higher mean diffusivity than both occasional and never users. Furthermore, daily users of high-potency cannabis had significantly higher mean diffusivity than daily low-potency users and those who never used or used weekly. Lastly, no statistically significant differences in corpus callosum mean diffusivity were noted between early onset and later onset users.

Another study examined the longitudinal changes in white matter microstructure after heavy cannabis use using diffusor tensor imaging [1561]. In this study, 23 young adult regular cannabis users and 23 age, sex-, and IQ-matched non-cannabis using controls with limited substance use histories were entered into the study. Cannabis use began prior to 17 years of age. The study findings suggested that cannabis use was associated with deficits in structural white matter in a number of different brain regions. These effects on white matter integrity were dose-dependent suggesting that continued heavy cannabis use during adolescence and young adulthood was associated with more profound white matter deterioration and contributed to functional impairment (e.g. verbal learning).

A more recent study that examined associations between a number of key variables (i.e. age at onset of cannabis use, duration of use, frequency of use and dose) and changes in white matter integrity reported that increased cannabis use was associated with a decrease in white matter integrity in selected brain areas [1562]. The study noted that changes (increases or decreases) in white matter integrity varied with age at onset of regular cannabis use, duration of use and current dose but not frequency of current use. Widespread changes in white matter integrity were noted within frontal, parietal and motor tracts with younger users having lower axial and radial diffusivity and older users having higher axial and radial diffusivity. Lower axial diffusivity is associated with reduced axonal volume while higher radial diffusivity is associated with reduced myelination; in other words, younger users showed decreased axonal volume, and increased myelination, while older users showed increased axonal volume, and decreased myelination. Importantly, previously unrecognized changes in white matter integrity associated with cannabis use were noted in older users (> 32 years of age). The authors suggest that exposure to lower potency cannabis during adolescence/early adulthood in combination with the effects of prolonged exposure to cannabis over many years results in disturbances in white matter integrity. Limitations of the study included its cross-sectional nature and a number of confounding factors including tobacco use, which was greater in the cannabis-using group vs. non-using group.

Another review of 31 studies examined the association between neuroanatomic alterations (especially in brain areas with high CB_1 receptor density) and regular cannabis use (i.e. daily, near-daily use) as well as association with level of use (i.e. dose, duration, age at onset of use) [1563]. The study found the existence of neuroanatomic alterations in brain areas high in cannabinoid receptors (i.e. hippocampus, prefrontal cortex, amygdala, cerebellum), and greater dose and earlier age of onset were associated with these alterations. The majority of cannabis users started smoking cannabis between age 15 and 17 and duration of use varied greatly across examined studies (i.e. 2 years to 23 years of regular use). Lifetime episodes of cannabis use ranged from 402 to 5 625. Several, but not all, of the included studies controlled for the confounding effects of alcohol and tobacco. Abnormalities in cannabis users compared to controls were most consistently observed in the hippocampus followed by prefrontal regions with very high cannabinoid receptor densities (i.e. the lateral prefrontal cortex and the anterior cingulate cortex). Overall, the most consistent neuroanatomic alterations included: (1) volumetric reductions in all regions (except cerebellum and striatum where increases were observed), (2) higher gray matter densities in most regions (i.e. amygdala, prefrontal cortex, parietal cortex, striatum); (3) altered shape, sulcal-gyral anatomy; and (4) cortical thickness. Principally, areas with the highest densities of cannabinoid receptors most consistently saw neuroanatomic alterations. Cannabis dosage was most consistently associated with neuroanatomical alterations in the hippocampus and the prefrontal cortex, and less consistently with the amygdala, striatum, parahippocampal gyrus, insula and temporal pole. Age of onset of cannabis use was most consistently associated with prefrontal neuroanatomy, and less consistently with neuroanatomical alterations in the parahippocampal gyrus, temporal cortex, and global brain measures. Duration of regular use was most consistently associated with neuroanatomical alterations in the prefrontal cortex and the hippocampus but not the amygdala, the parahippocampal gyrus, the cerebellum and the striatum. Taken together, the studies reviewed in this literature review suggest that regular cannabis use is associated with neuroanatomic alterations in several brain regions with the most consistent changes seen in the hippocampus (reduced volume and gray matter density, altered shape), followed by changes in the amygdala and striatum, orbitofrontal cortex, parietal cortex, insular cortex, and cerebellum. Furthermore, some associations were found between higher cannabis dosage and hippocampal alterations and between earlier age of onset and alterations in the prefrontal cortex. The authors also mention preliminary evidence suggestive of a protective effect of CBD and toxic effect of THC in the hippocampus, cerebellum, prefrontal and lingual regions. In conclusion, early onset of use, duration of use, dose and relative ratio of THC to CBD were all associated with neuroanatomical alterations in various brain regions.

A recent review looked at the effects of cannabis use on brain structure and function from (mainly cross-sectional) imaging studies [1564]. The review made the following conclusions: (1) smaller hippocampal volumes in cannabis users relative to healthy controls has been one of the most consistently reported findings; (2) there is an inverse relationship between cannabis use and hippocampal volume; (3) dose and duration of cannabis use appear critical for effects of cannabis on hippocampal volume; (4) cannabis use is associated with smaller orbitofrontal cortex volumes; (5) early onset cannabis use interacts with adolescent developmental events leading to disruption of normal neurodevelopmental processes (e.g. pruning and plasticity); (6) pre-existing vulnerabilities interact with dose, duration, and onset of cannabis use to determine outcomes; (7) cannabis use is associated with less efficient and less mature white matter microstructure in the genu, rostrum, and splenium of the corpus callosum as well as the superior longitudinal fasciculus and arcuate fasciculus; (8) combined cannabis and alcohol use resulted in significantly greater alterations in white matter tracts (i.e. in the superior longitudinal fasciculus, right posterior thalamic radiations, right prefrontal thalamic fibres, right superior temporal gyrus, right inferior longitudinal fasciculus, and left posterior corona radiata); (9) early onset and more intense cannabis use during adolescence is linked to less brain activation, with users who started in later adolescence showing higher brain activation compared to earlier onset users; (10) cannabis use is associated with increased recruitment of additional brain regions not typically utilized to compensate for deficits in other regions.

A recent systematic review and meta-analysis of 69 cross-sectional studies (2 152 cannabis users/6 575 non-users) in adolescents and young adults (≤ 26 years of age) reported that frequent/heavy cannabis use was associated with a small effect size for reduced cognitive functioning relating to delayed memory, attention, and speed information processing (d, -0.25; 95% CI, -0.32 to -0.17). The effect size diminished, however, following 72 hours of abstinence, (d, -0.08; 95% CI, -0.22 to 0.07), suggesting that any acute cognitive impairment from cannabis use may be restored after three days of abstinence. No greater deficits were observed in adolescents compared to young adults. Key limitations of these findings are related to the cross-sectional design (causality not established) and unaccounted variables in analyses (e.g., previous duration of use, cognitive functioning prior to cannabis use) [1565].

A recent literature review on THC potency supports that higher levels of potency, compared to lower levels, is associated with greater risk of cannabis use disorder, psychosis, acute cognitive impairment (especially in tasks that measured motor control and executive functioning), and structural changes of white matter in the corpus callosum. The authors recommend clinicians to not only ask and monitor patients' generic cannabis use frequency and duration, but also the specific concentrations of THC being used to better assess its adverse effects and risks. Within the context of prescribing cannabis for medical purposes, clinicians should weigh the potential risks of higher potency cannabis relative to its potential therapeutic effects [1566].

7.7.2 Psychomotor performance and driving

- ***Evidence from experimental clinical studies suggests acute use of (THC-predominant) cannabis impairs a number of psychomotor and other cognitive skills needed to drive a motor vehicle.***
- ***While chronic/frequent cannabis use may be associated with a degree of tolerance to some of the effects of cannabis in some individuals, chronic cannabis use can still pose risks to safe driving due, in part, to significant body burden of THC leading to a chronic level of psychomotor impairment.***
- ***Evidence from clinical and epidemiological studies suggests a dose-response effect, with increasing doses of THC increasing the risk of motor vehicle crashes that can lead to injuries and death.***
- ***Combining alcohol with cannabis (THC) is associated with an increased degree of impairment and increased risk of harm.***

It is well known from studies carried out among non-medical cannabis users that exposure to THC-predominant cannabis and psychoactive cannabinoids impairs psychomotor performance [140, 150, 238] and patients must be warned not to drive or operate complex machinery after acute consumption of smoked/vapourized or orally-ingested cannabis or consumption of psychoactive cannabinoid medications (e.g. dronabinol, nabilone, nabiximols) until a sufficient amount of time has elapsed to allow for safe driving. There is also now increasing evidence of chronic impairment associated with longer-term, frequent cannabis use (even with abstinence) that may also affect the ability to safely drive ([150, 229, 692, 1567, 1568] and see below).

Evidence from human *post-mortem* studies shows that the brain can accumulate relatively high concentrations of THC and 11-hydroxy-THC, while the concentrations of these cannabinoids remain much lower in blood [458]. In this study, 12 paired *post-mortem* samples of blood and brain from individuals involved in fatal motor vehicle accidents were examined. In one case, THC concentration in the brain was 19.4 ng/g, while the blood concentration of THC was 4.4

ng/mL. In another case, brain THC concentration was 29.9 ng/g where the THC concentration in the blood was ≤ 0.2 ng/mL [458]. Furthermore, examination of specific brain areas showed significant accumulation of THC and 11-hydroxy-THC in the substantia nigra, hippocampus, the occipital lobe, the striatum-putamen-pallidum, the frontal lobe, spinal cord and corpus callosum, the cortex and the white matter [458]. These findings show that despite low to near undetectable blood levels of THC and 11-hydroxy-THC, these psychoactive cannabinoids can accumulate in a number of brain areas associated with thinking, decision-making/executive function, vision, memory and coordination and which play an important role in the safe operation of a motor vehicle.

Cannabis

A review article looking at the impairing psychomotor effects of cannabis on driving found that psychomotor testing performance is decreased for up to five to six hours after smoking cannabis, with the majority of impairment occurring in the first two hours after smoking, although others suggest a window of at least three to six hours after smoking [238]. Given the variability in the data and the emergence of new studies with higher potency cannabis showing persistence of some psychoactive effects (e.g. sedation) up to eight hours after last inhalation, the authors of the study recommend that patients abstain from driving for a minimum of eight hours after achieving a subjective "high" from cannabis use, though the minimum waiting time may, for example, be longer in those that consumed cannabis orally as the onset of intoxication and psychomotor impairment is delayed compared to inhalation and lasts longer.

Clinical studies

<u>Acute</u>

Clinical studies have shown that acute cannabis administration (i.e. THC) affect areas of the brain involved in perception, attention, concentration, inhibitory/impulsivity control, executive control/decision-making, awareness, alertness, and coordination, all of which are required to safely operate a motor vehicle, although chronic cannabis users may develop tolerance to some, but not all, of the intoxicating/impairing effects associated with acute cannabis use [150, 238]. Some of these effects may also persist beyond the period of acute intoxication, especially in chronic/frequent users [150].

One clinical laboratory study reported that THC doses between 40 µg/kg and 300 µg/kg cause a dose-dependent reduction in performance on laboratory tasks measuring memory, divided and sustained attention, reaction time, tracking and motor function [154].

Another clinical study evaluated the psychomotor and neurocognitive effects of acute exposure to smoked cannabis as a means to evaluate the acute effects of cannabis on skills needed to drive safely (i.e. accurately controlling a car and reacting quickly to events on the road) [204]. Domains examined included psychomotor function, working memory, risk taking, and subjective and physiological effects in frequent and occasional cannabis smokers following controlled smoking of a 6.8% THC cigarette (i.e. 54 mg total available THC in the cigarette) up to 22.5 h after smoking. Frequent smokers smoked on at least four occasions weekly, while occasional smokers smoked less than twice per week. Mean blood THC concentration at 0.5 h post-smoking was 32 ng/mL in frequent smokers and 17.4 ng/mL in occasional smokers. At six hours, frequent smokers had a blood THC concentration of 4.1 ng/mL while most subjects classified as occasional smokers had blood THC concentrations under 1.3 ng/mL. At 24 h, all occasional smokers' blood THC concentrations were below the limit of detection, while frequent smokers had a mean blood THC concentration of 2.9 ng/mL. Occasional smokers had significantly higher scores on measures of "high" and "stimulated" as well as more intense anxiety. Significantly higher scores were also reported by occasional users on measures of "difficulty concentrating" (at three hours) and "altered sense of time" (at three and four hours). The authors found that cannabis smoking significantly impaired psychomotor function up to 3.5 h after smoking a 6.8% THC cigarette. Cannabis smoking appeared to impair psychomotor function (tracking error, hits, false alarms and reaction time) to a greater degree in occasional smokers compared to frequent smokers, raising the possibility of tolerance to some of the impairing effects of cannabis in frequent smokers. Occasional smokers also reported significantly longer and more intense subjective effects compared with frequent smokers who had higher blood THC concentrations.

A case cross-over study that examined whether acute cannabis use leads to an increased collision risk among 860 drivers that presented to emergency departments in Toronto and Halifax with an injury from a traffic collision found that 11% of the presenting drivers (95% CI = 9.0 – 13.1) reported using cannabis before driving [1569]. Regression analysis that measured exposure with blood and self-report data found that cannabis use alone was associated with a four-fold increase (OR = 4.11; 95% CI = 1.98 – 8.52) in odds of a collision. Those individuals who used cannabis before driving were also more likely to be male (91%). Ethanol consumption was associated with an increase in the odds of a crash (OR = 3.89, 95% CI = 1.86 – 8.09).

A randomized, double-blind, placebo-controlled clinical study examined the acute effects of two different doses of THC (13 mg vs. 17 mg) on cognitive-motor skills (i.e. speed and accuracy), cognitive flexibility, decision-making ability, and time and distance estimation (i.e. from an approaching car) in regular cannabis users [1369]. Fourteen subjects that used cannabis on a daily basis for at least five years were recruited into the study. The 17 mg THC dose was associated with a significant increase in collisions against the walls in the virtual maze task, whereas the effects of both THC doses were also significant in some of the cognitive flexibility tests. A significant increase in a risk-taking task was also noted with the higher 17 mg THC dose. Effects of THC on subjective ratings of "satisfaction", "pleasure", "high", and "drug effect" were significantly increased in subjects on either the low (13 mg) or high (17 mg) THC dose compared to the placebo. These results appear to support a dose-response effect of THC on cognitive impairment affecting faculties required for safe operation of a motor vehicle. For reference purposes, a recent study estimated that the mean weight of cannabis in a joint is 300 mg [589]. As such, a 300 mg joint with a potency of 4.3% THC would deliver 13 mg of THC whereas a 300 mg joint with a potency of 5.7% would deliver a 17 mg dose of THC.

A randomized, double-blind, placebo-controlled, crossover clinical study examined the acute effects of varying potencies of cannabis on ratings of a variety of subjective effects (i.e. intensity and duration of effects) [495]. One gram joints containing increasing doses of THC (i.e. 29 mg, 49 mg, and 69 mg) having respective THC potencies of 9.75%, 16%, or 23% THC in a group of regular non-medical cannabis users showed a strong effect of high-potency cannabis on ratings of subjective effects. Participants reported using an average of 7.7 joints per month in the past-year with an average duration of cannabis use of 7.7 years. Smoking of the low dose (29 mg THC) was associated with a mean serum THC C_{max} of 120 ng/mL and a maximum "high" score of just under 60 on the VAS scale, smoking of the medium dose (49 mg THC) was associated with a mean serum THC C_{max} of 160 ng/mL and was associated with a maximum "high" score of just over 60 on the VAS scale, whereas smoking of the highest dose (69 mg THC) was associated with a mean serum THC C_{max} of 190 ng/mL and a maximum "high" rating of 80 on the VAS scale, further supporting a dose-response effect. While blood levels of THC declined rapidly and fell under 25 ng/mL within two hours post-dose at the highest dose, subjective ratings of "high" declined far more gradually and persisted for longer compared to the blood levels of THC. The scores on the VAS for dizziness, dry mouth, palpitations, impaired memory and concentration, down, sedated and anxious feelings reached maximum within the first two hours post-dose. THC dose effect was significant. At almost two hours after smoking the highest dose, participants who smoked the highest potency cannabis cigarette reported being much less alert, content and calm compared to those having smoked placebo. At four hours post-dose, scores of "feel a drug effect" rose correspondingly with increasing THC doses with significant differences between THC treatment conditions relative to placebo and between the high dose and the low dose. THC-induced decrease in stimulation and increase in anxiety lasted up to eight hours post-smoking. Overall, the study findings indicate that psychoactive and cognitive effects were most pronounced in the first two hours post-dose, although a significant increase in sedation was still measurable eight hours post-dose. The maximum rating of "high" was reached within minutes in all dose conditions, but was 1.4 times higher with the high THC dose (69 mg) than with the low dose (29 mg). The rating of dizziness doubled with the highest dose compared to the middle and low doses (29 and 49 mg THC) up to two hours post-smoking. Sedation was increased by almost six-fold with the highest THC dose (69 mg) compared to placebo. The subjective effects were felt as unpleasant with the middle and high THC doses, relative to the low dose (29 mg) which received the highest score on "like the drug" and "want more of the drug".

A double-blind, placebo-controlled, crossover study comparing the acute effects of a medium dose of dronabinol (20 mg) and of two cannabis 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 [1570]. A "moderate" dose (21 mg of THC) was associated with impairments in motor and perceptual skills necessary for safe driving [1571]. 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 [221]. 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 [1572, 1573]. Others disagree with this assertion [231, 1574].

A double-blind, placebo-controlled, randomized, three-way, crossover design study suggested that acute 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 one to three joints per day, > 160 times per year) [1575]. However, the magnitude of the impairment appeared to be less in heavy users, possibly due to tolerance. The authors indicate that driving impairments after dronabinol were of clinical relevance and comparable to drivers operating their vehicles at a blood-alcohol (BAC) concentration of greater than 0.8 mg/mL (0.08 g%). Approximately 25% of the "heavy users" demonstrated impairment equivalent to, or worse than, that reported for drivers with a BAC 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) [230, 1575].

Chronic

There is also emerging evidence coming from studies with frequent, chronic non-medical cannabis users, having a high body load of THC, that report blood THC levels above 5 ng/mL (considered to be an "impairing" dose) for periods lasting several days after last THC exposure [229]. These emerging findings raise the possibility of a persistent level of impairment that may last as long as three to seven days after last use in chronic, frequent (heavy) users of cannabis that may affect psychomotor skills needed for safe driving.

A clinical laboratory study that assessed the psychomotor function in chronic, daily cannabis smokers during three weeks of continuously monitored abstinence on a secure research unit found that performance on critical tracking and divided attention tasks was impaired even after three weeks' abstinence [1567]. In this study, 19 male, chronic, daily cannabis smokers who self-reported consuming 11 cannabis joints per day for the last 10 years (at least five days/week for six months prior to admission) were compared to a control group of occasional cannabis and/or MDMA users with regards to performance on two psychomotor tests: the critical tracking task which measures a subject's perceptual motor control and which has been demonstrated to be sensitive to the impairing effects of THC, and the other test being the divided attention task which assesses the ability of the individual to divide attention between two tasks performed simultaneously and which has also been demonstrated to be sensitive to the impairing effects of THC. Mean plasma THC and 11-hydroxy-THC levels on admission were 5.3 ng/mL and 2.1 ng/mL respectively while on day 8 after admission were 1.3 and 0.2 ng/mL respectively. Values for THC fell below 1 ng/mL on days 14 to 16. The findings showed that psychomotor performance (the critical tracking task and divided attention task) of chronic, daily cannabis smokers improved over three weeks of abstinence but remained significantly poorer than performance of the control group of occasional cannabis and MDMA users. The authors hypothesize that the observed persistent psychomotor impairments could have arisen from withdrawal effects, from residual THC concentrations in the blood as a result of heavy body burden of THC and release from peripheral stores, or lastly from the effects of cumulative lifetime intake reflecting persistent changes in psychomotor function in chronic cannabis smokers.

A study that characterized cannabinoid elimination in blood from 30 male daily chronic cannabis smokers during monitored sustained abstinence for up to 33 days on a closed residential unit found that both THC and its inactive metabolite 11-nor-9-carboxy-THC were detected in blood up to one month after last smoking, which was reported by the authors as being four times longer than previously described [459]. The study also reported that males had a shorter maximum detection window of 11-hydroxy-THC (72 h) compared with females (seven days). The vast majority of the participants were THC-positive on admission with a median concentration of 1.4 ng/mL of THC in the blood and the levels of THC decreased gradually over time.

A study examined the plasma cannabinoid detection windows for chronic frequent cannabis smokers and also attempted to determine if plasma concentrations of cannabinoids were correlated with psychomotor performance in critical tracking and divided attention tasks [229]. Twenty-eight male participants who reported smoking an average of 10.6 joints per day (range: 1 – 30) for an average of 10.6 years (range: 4 – 28) and who abstained from cannabis smoking for a period of up to 30 days, had a baseline median range of blood THC on admission of 4.2 ng/mL. Blood THC concentrations significantly decreased 24 h after admission. Three days after admission, a significant number of participants had blood THC levels ≥ 5 ng/mL, while seven days after admission almost 30% of participants had blood THC levels greater than 2 ng/mL. One participant had a plasma THC concentration of ≥ 2 ng/mL for 18 consecutive days. THC was detected in some specimens as late as 30 days after admission (0.3 – 1.3 ng/mL). Years of prior cannabis use significantly correlated with THC concentration on admission. Tracking error was correlated with THC, 11-hydroxy-THC, and 11-nor-9-carboxy-THC at baseline and with 11-hydroxy-THC on day 8. No other outcome measures such as divided attention task or critical tracking task were significantly correlated with cannabinoid concentrations. Based on the findings of this study, the authors argue against the utility of detectable THC and 11-hydroxy-THC in the plasma of chronic frequent cannabis smokers as a reliable marker for *recent* cannabis use. Blood levels of 11-hydroxy-THC never appeared to exceed 2 ng/mL beyond 24 h, which the authors suggest could be a cut-off for *recent* cannabis use (within 24 h). The authors suggest that residual THC in plasma weeks after last smoking may be associated with impairment in frequent chronic cannabis smokers. Furthermore, they suggest that although partial tolerance may develop to some impairing effects of cannabis smoking among chronic frequent cannabis smokers, some residual impairment may limit the appropriate operation of a motor vehicle or mechanical equipment which could result in injury or in criminal litigation.

Epidemiological studies

A case-control study estimating accident risk for a variety of substances including alcohol, medicines, and illegal drugs found that the OR for accident risk for all the THC concentrations measured (1 to > 5 ng/mL) was statistically significant [1576]. At whole-blood concentrations of ≥ 2 ng/mL THC, the risk of having an accident was significantly increased. One study found that the risk of responsibility for fatal traffic crashes while driving under the influence of cannabis (DUIC) 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 OR 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 [1577]. The findings from this study further support the notion of a causal relationship between cannabis use and crashes [1577].

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) [1578]. Using a binary logistic regression model, the OR for being judged impaired appeared to increase with increasing drug concentrations from 2.9 ng/mL onwards. 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 [154, 1576].

A meta-analysis of observational studies examining acute cannabis consumption and motor vehicle collision risk reported that DUIC was associated with a significantly increased risk of motor vehicle collisions compared with unimpaired driving, with an OR of 1.92 (95% CI = 1.35 – 2.73) [230]. Collision risk estimates were higher in case-control studies and studies of fatal collisions, than in culpability studies and studies of non-fatal collisions. It has been reported that individuals who drive within one hour of using cannabis are nearly twice as likely to be involved in motor vehicle accidents as those who do not consume cannabis [1571]. 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 [230]. 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 [230]. 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 [230].

A 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 [232]. 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.

Use for medical purposes and driving

A pilot, prospective, multicentre, non-interventional post-marketing surveillance study conducted to collect data on driving ability, tolerability and safety from 33 patients with MS starting nabiximols treatment reported that a four to six-week treatment period with nabiximols (average 5.1 sprays per day, or 13.7 mg THC and 12.8 mg CBD/day) was associated with a statistically significant improvement in self-rated spasticity and was also *not* associated with a statistically significant deterioration in patients' ability to drive, as measured in the laboratory using a battery of cognitive and psychomotor tests [692]. However, less than half of the patients met the "fit to drive" criteria. In addition, 4 out of the 33 patients experienced a non-serious, mild or moderate adverse event associated with nabiximols treatment (e.g. dizziness and vertigo).

Cannabis and alcohol

Clinical studies

A within-subject, blinded, placebo-controlled driving simulator study examined the subjective feelings and driving abilities in 14 healthy students after smoking two different cannabis cigarettes of varying potencies (13 and 17 mg THC) or after alcohol intake (0.5 g/kg of body weight to a BAC of 0.05%) [1579]. All participants were low to moderate users of cannabis and alcohol, with a reported cannabis use of one to four times per month. While both alcohol and the lower dose of THC (13 mg) significantly increased reaction time compared to placebo, the magnitude of the effect was greater with the higher THC dose (17 mg). No residual effect on reaction time was found 24 h after smoking the highest THC dose. Compared to placebo, both the low (13 mg) and high (17 mg) THC doses significantly slowed average driving speed in a dose-dependent manner, while alcohol increased it. Both the low and high THC doses significantly increased lane position variability compared to placebo, while only the low THC dose significantly increased steering wheel deviations. Average speed, lane position variability and steering wheel deviation returned to baseline levels 24 h post-smoking. There also appeared to be a dose-dependent increase in the number of collisions with an apparent two-fold increase in the number of individuals having a collision with only a modest increase in the amount of THC administered (i.e. 4 mg or a 23% increase in THC). Subjective effects were also examined and the study found a significant increase in physical discomfort, physical effort, and lack of energy with the highest dose of THC compared to placebo, although the lowest dose also produced physical discomfort and effort. Although both the lowest THC dose (13 mg) and alcohol (0.05% BAC) appeared to produce driving impairment, there appeared to be differences in subjective effects between THC and alcohol.

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 [231]. The level of THC detected in the blood was higher when cannabis was consumed along with alcohol than when consumed alone. It also appeared that regular cannabis users displayed more driving errors than non-regular cannabis users.

A double-blind, randomized, placebo-controlled, within-subject experimental driving simulator study with 18 subjects that self-reported using cannabis occasionally (≥ once in the last three months, ≥ three days/week) determined how blood THC concentrations were related to driving impairment with and without alcohol [228]. The study found that vapourized cannabis (0.5 g dried vapourized cannabis with a THC concentration of either 2.9% THC, or 6.7% THC or 14.5 mg THC or 33.5 mg THC), when combined with alcohol (0.065% peak breath alcohol concentration), increased standard deviation of lateral position (SDLP) similar to 0.05 and 0.08% BAC. Furthermore, the effects of alcohol and cannabis on SDLP were additive rather than synergistic with 5 ng/mL THC and 0.05% BAC showing similar SDLP as 0.08% BAC alone.

A randomized, placebo-controlled, blinded clinical study that evaluated acute cannabinoid disposition in blood and plasma after controlled vapourized cannabis administration with and without low-dose oral alcohol administration found that low-dose oral alcohol administration significantly increased median maximum (C_{max}) blood THC and 11-hydroxy-THC concentrations [206]. Nineteen healthy participants that self-reported consuming cannabis ≥ one time/three months but ≤ three days/week over the past three months (i.e. occasional use) completed all arms of the study. Vapourization of 0.5 g of dried cannabis flowers containing a low dose of THC (2.9% THC, 0.22% CBD) without any oral alcohol administration was associated with a median maximum blood (C_{max}) THC level of 32.7 ng/mL, whereas vapourization of cannabis containing a high dose of THC (6.7% THC, 0.37% CBD) was associated with a median THC C_{max} of 42.2 ng/mL. Under the same conditions, the median C_{max} of 11-hydroxy-THC with the low THC dose was 2.8 ng/mL, whereas with the high THC dose the median C_{max} of 11-hydroxy-THC was 5.0 ng/mL. Time to maximum THC and 11-hydroxy-THC blood levels was 10 min. Co-administration of an oral alcohol dose producing a breath alcohol concentration of 0.065% along with vapourization of the low THC dose was associated with median C_{max} of THC of 35.3 ng/mL, whereas with the high THC dose the median THC C_{max} was 67.5 ng/mL. With co-administration of alcohol, the median C_{max} of 11-hydroxy-THC under the low THC dose was 3.7 ng/mL, whereas under the high THC dose the median C_{max} of 11-hydroxy-THC was 6.0 ng/mL. These results suggest that co-consumption of alcohol with THC can result in significantly elevated concentrations of blood THC and 11-hydroxy-THC compared to THC alone that may contribute to increasing cognitive impairment which can compromise safe driving abilities. The authors of the study also suggest that vapourization of cannabis under the study conditions delivered THC in a similar manner to smoking and producing similar cannabinoid concentration profiles. Factors that affected vapourized THC delivery included heating temperature, number of balloon fillings, cannabis amount and blend, and length of time between volatilization and inhalation (i.e. possible adherence of THC to the balloon surface). Participants appeared to require less self-titration at the lower THC dose and more self-titration at the higher THC dose, which was reflected in greater blood THC variability under the high THC dose condition.

Epidemiological studies

A follow-up study investigated the effects of alcohol (0.05% BAC), THC (13 mg), and their combination on driving and non-driving tasks as well as the extent to which people are willing to drive based on their subjective sensations and their perceived effects of the drugs [220]. Combining alcohol and THC resulted in a greater number of participants having collisions in a driving simulator task compared to alcohol or THC alone or placebo. Lane position variability increased significantly under the combined effects of alcohol and THC relative to the other treatments, which did not differ from each other. The combination of alcohol and THC caused a significantly greater sensation of “sedation” in comparison to all other treatments. Furthermore, the combination of THC and alcohol had significant and intense effects on particular dimensions of the Swedish Occupational Fatigue Inventory such as “lack of energy”, “physical exertion”, and “lack of motivation”. Based on the study findings, the authors suggest that the subjects felt that the combination of alcohol and

THC was the most potent treatment and had an additive effect on some of the subjective sensations compared to the effects of the two drugs in isolation. No residual effects of any treatment were observed 24 h after treatment.

A case-control study that examined driver crash data compiled by the U.S. National Center for Statistics and Analysis of the National Highway Traffic Safety Administration over a period of 17 years (1991 – 2008) found that the prevalence of THC and alcohol in car drivers aged 20 years and older involved in a fatal crash has increased approximately five-fold, from below 2% in 1991 to above 10% in 2008 [1372]. Furthermore, the authors of the study reported that each 0.01 BAC unit increased the odds of an unsafe driving action, a proxy measure of crash responsibility, by approximately 9 to 11%. After adjusting for driver age, sex, alcohol, polydrug use, and previous driving record, drivers who were positive for THC alone had a 16% increased odds of an unsafe driving action. When alcohol and THC were combined, the odds of an unsafe driving action increased by approximately 8 to 10% for each 0.01 BAC unit increase over alcohol or THC alone. Drivers at typical BAC legal limits of 0.05 and 0.08 had greater odds of committing an unsafe driving action of 66% and 117% respectively when compared with sober, THC-free drivers. However, the authors suggest that when combined with THC these odds increased to 81% and 128% respectively. Furthermore, the THC and alcohol combination effect was most pronounced at the lowest levels of BAC. In other words, as BAC level increases, the impairing effects of alcohol dominate the THC-alcohol relationship. The authors concluded that drivers positive for both alcohol and THC had greater odds of making an error than drivers positive for either alcohol or cannabis alone.

Lastly, data from an annual repeated cross-sectional survey of Ontario adults that surveyed over 16 000 adults and recorded the incidence of self-reported collisions among drivers who reported driving under the influence of alcohol (DUIA) and DUIC found that drivers who reported neither a DUIA or a DUIC had the lowest prevalence of collisions (6.7%) [1580]. However, those reporting either a DUIA or a DUIC reported a significantly higher prevalence of collision involvement of 9.6%. The highest likelihood of collision involvement was found among drivers reporting both behaviours (30.5%). In other words, those who reported both a DUIC *and* a DUIA were more than three times as likely to be involved in a collision compared to those who reported one or the other behaviour (OR = 3.65, CI = 2.12 – 6.28).

7.7.3 Psychiatric effects

7.7.3.1 Anxiety, PTSD, depression and bipolar disorder

- ***Evidence from clinical studies suggests a dose-dependent, bi-phasic, effect of THC on anxiety and mood, where low doses of THC appear to have an anti-anxiety and mood-elevating effect whereas high doses of THC can produce anxiety and lower mood.***
- ***Epidemiological studies suggest an association between (THC-predominant) cannabis use, especially chronic, heavy use and the onset of anxiety, depressive and bipolar disorders, and the persistence of symptoms related to PTSD, panic disorder, depressive disorder, and bipolar disorder.***
- ***Preliminary evidence from surveys suggests an association between use of ultra-high-potency cannabis concentrate products (e.g. butane hash oil, BHO) and higher rates of self-reported anxiety and depression and other illicit drug as well as higher levels of physical dependence than with high-potency herbal cannabis.***

Anxiety and depression

Epidemiological studies suggest a possible association between regular cannabis use and the development of anxiety and depression, however the available evidence of a link between cannabis use and anxiety/anxiety disorders and depression is more mixed and less consistent than that seen between cannabis use and psychosis [162]. That being said, depression and anxiety disorders appear to be not only associated with cannabis dependence but are also predictive of whether individuals transition from use to dependence [162]. It appears that THC can exert bi-directional effects on anxiety and mood (i.e. anti-anxiety and mood-elevating effects at low doses, and anxiogenic and mood-lowering effects at higher doses), and ECS dysfunction, such as that caused by chronic, high-level activation of CB_1 receptor signaling (or conversely CB_1 receptor antagonism), especially during adolescence, can increase or exacerbate the risk for anxiety/anxiety disorders and depression [1581, 1582]. More recently, a few cross-sectional surveys have explored the effects of ultra-high potency cannabis concentrate products such as butane hash oil (BHO) on various psychiatric outcomes. In one study of 83 867 cannabis users, of which 5 922 reported using BHO, participants who reported a lifetime diagnosis of depression (OR = 1.15, p = 0.003), anxiety (OR = 1.72, p < 0.001) and other substance use (OR = 1.29, p < 0.001) were more likely to use BHO than only high potency herbal cannabis [1583]. In addition, BHO users reported stronger negative effects and less positive effects with BHO compared to high potency herbal cannabis. In another study, more frequent BHO use was associated with higher levels of physical dependence (RR = 1.8, p < 0.001, adjusted RR = 1.2, *p* = 0.014), which remained significant even after adjustment for confounders [520]. While there was an association between BHO use and impaired control (RR = 1.3, p < 0.001), cannabis-related academic/occupational problems (RR = 1.5, p = 0.004), poor self-care (RR = 1.3, p = 0.002) and cannabis-related risk behaviour (RR = 1.2, p = 0.001), these associations did not persist after controlling for confounding factors.

Anxiety

Anecdotal claims of cannabis use to relieve anxiety have been postulated to actually result from a so-called "stress-misattribution hypothesis" which posits that cannabis users may potentially be misattributing symptoms of stress or tension to anxiety [1582, 1584]. Under this hypothesis, affected individuals believe they are using cannabis to relieve symptoms of anxiety, reporting using cannabis to self-medicate, while in actuality experiencing not anxiety, but stress (i.e. tension, irritability, persistent symptoms of arousal) as well as, or instead of, symptoms of anxiety [1582, 1584].

The available evidence suggests a role for the ECS in modulating anxiety responses, under both basal non-aversive environmental conditions, but also under aversive or stressful environmental conditions [177]. Pharmacological enhancement of endocannabinoid signalling under aversive/stressful conditions in various animal models of anxiety either through inhibition of endocannabinoid degradation or through blockage of endocannabinoid re-uptake has been generally associated with anxiolysis mainly through a CB_1 receptor-dependent mechanism [177].

Cannabis use, especially cannabis containing mainly THC, dose-dependently affects anxiety behaviours, with low doses generally being anxiolytic and high doses either ineffective or potentially anxiogenic [177]. Indeed, consumption of THC-predominant cannabis has been shown to cause an acute and short-lasting episode of anxiety in approximately 20 – 30% of users [1584], often resembling a panic attack; this is more often encountered in naïve cannabis users and those who consume higher doses of cannabis or THC (e.g. > 5 mg oral Δ^9-THC), and also when cannabis is consumed in novel or stressful environments [189, 191]. 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 [1585-1588], there is some evidence that cannabis or cannabinoids may be useful in treating anxiety or depression *secondary* to other disorders (e.g. chronic pain, PTSD). In addition, while there is much pre-clinical evidence to suggest a role for CBD as an anxiolytic, there is less but emerging clinical evidence to suggest a potential role for CBD in alleviating social anxiety [171, 1589] and additional research is required. For more information on potential therapeutic uses of cannabis or cannabinoids, such as CBD, in the treatment of anxiety and depression, please consult **Section 4.9.5.1**.

Recent studies suggest the use of cannabis among individuals with anxiety disorders is associated with worsening of mental health-related functions. One study reported that mental health-related QoL was significantly lower among individuals with anxiety disorders who were also using cannabis [1590]. Data for this study was gathered from the **NESARC** where face-to-face interviews were conducted with over 43 000 U.S. adults ages 18 and older from the civilian non-institutionalized population. Anxiety disorders included in this study referred to panic disorder, social anxiety disorder, specific phobia, and generalized anxiety disorder (GAD) in the last 12 months. "Regular cannabis use" was defined as use that was at least weekly and "occasional use" was defined as use that was less than weekly. Compared to non-users, both female and male regular cannabis users reported significantly more often that their emotional or physical problems interfered with social activities, they accomplished less because of emotional problems, and they performed work or other activities less carefully because of emotional problems. They also reported feeling peaceful and calm less often and tended to feel depressed more often. In contrast, few differences were found between occasional cannabis users and non-users in mental health-related QoL, although female occasional cannabis users reported feeling peaceful less of the time. Among males with anxiety disorders, occasional cannabis users reported feeling peaceful and calm more frequently than regular cannabis users, feeling depressed less often than regular cannabis users and feeling less interference with social activities compared to regular users. In contrast, regular cannabis use was associated with significantly poorer mental health-related QoL for both males and females compared to non-users. Regular cannabis use was also associated with significantly lower mean mental health scores among both males and females, and lower mean scores on subscales of social functioning among females and mental health, and role emotional subscales among males compared to occasional cannabis use. Linear regression analyses examining associations between levels of cannabis use and mental QoL showed significantly poorer mental QoL among regular, but not occasional cannabis users and was applicable to both females and males. The authors conclude that regular, but not occasional, cannabis use among individuals with anxiety disorders is associated with poorer mental health-related QoL and argue against the self-medication hypothesis.

A fifteen-year representative longitudinal cohort study among 1 943 individuals examining the association between adolescent cannabis use and common mental disorders into young adulthood reported no consistent associations between frequency of adolescent cannabis use and depression (i.e. major depressive episode) at age 29 years [1591]. However, daily cannabis use was associated with a more than two-fold increased risk of anxiety disorder at age 29 (AOR = 2.5; 95% CI = 1.2 – 5.2), as was cannabis dependence (AOR = 2.2; 95% CI = 1.1 – 4.4). Among weekly and more than weekly (i.e. daily) adolescent cannabis users that continued daily cannabis use at 29 years, there was still a significant increased odds of anxiety disorder (AOR = 3.2; 95% CI = 1.1 – 9.2). Early, regular cannabis use in adolescence increased the risk of anxiety disorder at age 29, with slightly higher risks if regular use also occurred at 29 years.

A systematic literature review and meta-analysis, using data from 31 studies on samples drawn from 112 000 cases from the general population of 10 countries, quantitatively assessed the relationship between anxiety (i.e. anxiety diagnoses with or without comorbid depression according to DSM/ICD diagnostic criteria) and cannabis use [1592]. The study reported a small positive association between anxiety and either cannabis use (OR = 1.24; 95% CI = 1.06 – 1.45; p = 0.006; N = 15 studies) or CUD (OR = 1.68; 95% CI = 1.23 – 2.31; p = 0.001; N = 13 studies), and between comorbid anxiety and depression and cannabis use (OR = 1.68; 95% CI = 1.17 – 2.40; p = 0.004; N = 5 studies). The positive association between anxiety and cannabis use (or CUD) was present in subgroups of studies with AORs for possible confounders and in studies with clinical diagnoses of anxiety. Cannabis use at baseline was also significantly associated with anxiety at follow-up in five studies (OR = 1.28; 95% CI = 1.06 – 1.54; p = 0.01). Individuals with various anxiety disorders and concurrent anxiety and depression were more likely to use cannabis or to have a CUD (i.e. dependence and/or abuse/harmful use) compared to those without anxiety disorders. The authors suggest that cannabis use could further exacerbate existing symptoms of anxiety depending on the genetic vulnerability, severity of anxiety symptoms, gender and age, among other factors. The findings are based on samples from the general population neither in treatment for anxiety nor for CUD.

A U.K. prospective, population-based cohort study (**ALSPAC**) of 4 561 individuals that investigated the associations between cannabis or cigarette use at age 16, and depression or anxiety at age 18, found weak evidence for an association between cannabis use and anxiety (unadjusted OR = 1.13, 95% CI = 0.98 – 1.31) that disappeared after fully adjusting for confounding factors (AOR = 0.96, 95% CI = 0.75 – 1.24) [1593]. Study limitations include (relatively) small sample size to detect a small effect, self-reported cannabis use, and assessment of outcomes by computerized interview.

A recent epidemiological study comparing data from two waves of the **NESARC** (2001 – 2002 and 2004 – 2005) and examining the relationship between cannabis use and risk of psychiatric disorders among 35 000 respondents, reported no association between past-year cannabis use and any anxiety disorder (OR = 0.9; 95% CI = 0.7 – 1.1) [512]. Limitations of the study include limited follow-up period (i.e. only three years), self-reported cannabis use, and limited categories of cannabis use frequency (i.e. no past-year cannabis use, some past-year cannabis use but less than one use episode per month, and greater than or equal to one use episode per month).

An epidemiological study providing the first nationally representative information on the prevalence and correlates of DSM-5 CUD using data from the 2012 – 2013 wave of the **NESARC-III** reported that past-year CUD was associated with any anxiety disorder (AOR = 2.8), and lifetime CUD was also associated with anxiety disorders (AOR = 2.9) [338]. Furthermore, the association between any anxiety disorder and past-year CUD increased with increasing severity of CUD (AOR = 2.2, 2.9, 4.4 for mild, moderate, and severe CUD respectively). The association between panic disorder/GAD and past-year CUD was particularly strong, with an AOR of 2.5, 2.8 and 6.6 (mild, moderate, severe CUD respectively) for panic disorder, and 3.0, 3.6, and 6.3 (mild, moderate, severe CUD respectively) for GAD.

Depression

Regarding depression, findings from pre-clinical studies suggest that reductions in ECS signaling are associated with depressive-like symptoms [177]. Pharmacological manipulation of the ECS resulting in elevation of anandamide for example, has been associated with anti-depressant-like behaviour in animal models of chronic stress [177].

One 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 [1594]. The authors also identified 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 [1595]. However, after adjusting for group differences, the association was no longer significant. In a follow-up 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 [1596].

In contrast, another U.S. study based on the results of the 2001 – 2002 **NESARC** (n = 43 093) found that major depression was significantly associated with lifetime cannabis disorders and dependence [1597]. A subsequent analysis of the same data examining the association between cannabis use and health-related QoL among individuals with depressive disorders found that women with depressive disorders who used cannabis regularly reported poorer mental QoL [170]. While the finding remained significant after adjusting for socio-demographic variables, it was not sustained after adjusting for comorbid anxiety disorders. Occasional cannabis use among women was not associated with lower QoL when compared with non-users. Little difference was noted among men with depressive disorders when comparing users to non-users.

A 2007 study using data from the **NE**therlands **ME**ntal Health **S**urvey and **I**ncidence **S**tudy (**NEMESIS**) found a modest increased risk of a first depressive episode (OR = 1.62; 1.06 – 2.48) associated with cannabis use, after controlling for strong confounding factors [1598]. Of greater significance in this study was the strong increased risk of bipolar disorder (OR = 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 systematic review and meta-analysis of population-based longitudinal studies or case-control studies, nested within longitudinal designs, examined the association between cannabis use and the risk of psychotic or affective mental health outcomes (e.g. depression, suicidal thoughts, and anxiety) [196]. The overall AOR for depression outcomes associated with most frequent use of cannabis compared with non-users was 1.49 (95% CI = 1.15 – 1.94). With regards to suicidal ideation, the study reported significant heterogeneity in the data and was not able to conduct a meta-analysis and provide an overall AOR.

An integrative analysis of four Australasian cohorts (i.e. the *Victorian Adolescent Health Cohort Study*, the *Personality and Total Health study*, the *Australian Temperament Project*, and the *Christchurch Health and Development Study*) that studied the relationships between the use of cannabis and the development of symptoms of depression from mid-adolescence to adulthood among more than 6 900 participants reported a small to moderate association between weekly cannabis use and symptoms of depression compared to non-use of cannabis (0.3 – 0.5 SD) [1599]. After adjustment for confounding factors, the association between weekly cannabis use and symptoms of depression persisted, though it was slightly reduced (0.24 SD; 95% CI = 0.18 – 0.30). The strength of the association between cannabis use and depression also varied with age—the associations were strongest in mid-adolescence and reduced to generally weak and negligible effects in mature adulthood.

A longitudinal cohort study of 45 087 Swedish male conscripts examining the association between cannabis use and mental disorders reported no association between frequency of cannabis use and risk of depression even in subjects with the highest level of cannabis use (after adjustment for potential confounders) [1600]. However, the study did report a strong graded association between cannabis use and schizoaffective disorder, with heavy use conferring the greatest risk (OR = 7.5; 95% CI = 3.4 – 16.7) compared to those who had never used cannabis.

A fifteen-year representative longitudinal cohort study among 1 943 individuals examining the association between adolescent cannabis use and common mental disorders into young adulthood reported no consistent associations between frequency of adolescent cannabis use and depression (i.e. major depressive episode) at age 29 years [1591]. However, daily cannabis use was associated with a more than two-fold increased risk of anxiety disorder at age 29 (AOR = 2.5; 95% CI = 1.2 – 5.2) as was cannabis dependence (AOR = 2.2; 95% CI = 1.1 – 4.4). Among weekly and more than weekly (i.e. daily) adolescent cannabis users that continued daily cannabis use at 29 years, there was still a significant increased odds of anxiety disorder (AOR = 3.2; 95% CI = 1.1 – 9.2). Early, regular cannabis use in adolescence increased the risk of anxiety disorder at age 29, with slightly higher risks if regular use also occurred at 29 years.

A systematic review and meta-analysis of 14 longitudinal studies examining the association between cannabis use and depression among a population of 76 058 subjects reported that the pooled OR for depression among individuals using cannabis compared with controls was 1.17 (95% CI = 1.05 – 1.30) [1016]. "Cannabis use" was defined as any cannabis use, monthly, or lifetime use on five occasions. Heavy cannabis use (defined as use meeting the DSM-IV criteria for CUD or alternatively at least weekly cannabis use), was associated with increased incidence of depression with a pooled OR = 1.62 (95% CI = 1.21 – 2.16). Depression was defined as including major depressive disorder, dysthymia, or depressive symptoms using validated clinical tools. The authors of the study concluded that cannabis use was associated with a modest increased risk of developing depressive disorders and that heavy cannabis use was associated with a stronger, but still moderate, increased risk for developing depression. Meta-regressions to detect any effect of age on the association between cannabis use and depression failed to show any effect, although the tests were underpowered because of the small number of studies included in the meta-analysis. The results of this systematic review and meta-analysis suggest the existence of a modest dose-dependent relationship between cannabis use and depressive symptoms. Limitations of the study included methodological and other limitations inherent in the primary studies included in the analysis.

A longitudinal study examined the influence of sub-clinical depressive symptoms on long-term functional and clinical outcomes in 64 first-episode psychosis patients who were cannabis users, and on the ability of patients to stop using cannabis [1601]. The study reported that the presence of sub-clinical depressive symptoms in first-episode psychosis patients during five years of follow-up was associated with continued cannabis abuse (β = 4.45, 95% CI = 1.78 – 11.17, p = 0.001) and with worse functioning (β = -5.50, 95% CI = -9.02 – -0.33, p = 0.009). The authors suggest that sub-clinical depressive symptoms should be treated in first-episode psychosis patients to prevent the development of an unfavorable clinical and functional course, especially in cannabis users.

A U.K. prospective, population-based cohort study (**ALSPAC**) of 4 561 individuals that investigated the associations between cannabis or cigarette use at age 16 and depression or anxiety at age 18 found that both cannabis (unadjusted OR = 1.5, 95% CI = 1.26 – 1.80) and cigarette use (unadjusted OR = 1.37, 95% CI = 1.16 – 1.61) increased the odds of developing depression; adjustment for confounding factors attenuated these relationships though evidence of association persisted for cannabis use (AOR = 1.30, 95% CI = 0.98 – 1.72), implying a slightly greater than two-fold increase in risk of depression with the highest level of self-reported cannabis use (> 60 times) compared to never users [1593]. Study limitations include (relatively) small sample size to detect a small effect, self-reported cannabis use, and assessment of outcomes by computerized interview.

A recent epidemiological study comparing data from two waves of the **NESARC** (2001 – 2002 and 2004 – 2005) and examining the relationship between cannabis use and risk of psychiatric disorders reported no association between cannabis use and any mood disorder (OR = 1.1; 95% CI = 0.8 – 1.4) [512]. Limitations of the study include limited follow-up period (i.e. only three years), self-reported cannabis use, and limited categories of cannabis use frequency (i.e. no past-year cannabis use, some past-year cannabis use but less than one use episode per month, and greater than or equal to one use episode per month).

An epidemiological study providing the first nationally representative information on the prevalence and correlates of DSM-5 CUD using data from the 2012 – 2013 wave of the **NESARC-III** reported that past-year CUD was associated with major depressive disorder (AOR = 2.8) and lifetime CUD was also associated with major depressive disorder (AOR = 2.6) [338]. Furthermore, the association between major depressive disorder and past-year CUD increased with increasing severity of CUD (AOR = 2.2, 3.1, and 4.2 for mild, moderate, and severe CUD respectively).

Bipolar disorder

Bipolar I and II disorders have been reported to occur in approximately 1 – 3% and 3 – 5% of the population, respectively [1602]. Bipolar disorders are also often complicated by co-occurring substance use disorders, which are associated with increased co-morbidities [1602]. More specifically, cannabis is one of the most frequently abused illicit drugs in people diagnosed with bipolar disorder [193, 1603-1606]. Lifetime cannabis use among bipolar patients appears to be around 70%, and approximately 30% of patients with bipolar disorder have a comorbidity of cannabis abuse or dependence – rates that exceed those observed in the total population [1607]. Cannabis use in bipolar disorder is also associated with poorer outcomes, increased symptom severity and poorer treatment compliance [1608]. The current available evidence suggests there is a significant relationship between cannabis use and subsequent exacerbation and onset of mania symptoms and that cannabis may worsen the course of bipolar disorder by increasing the likelihood, severity or duration of manic phases [1609]. While cannabis use often precedes first manic episodes, cannabis use is hypothesized to be a potential cause, and a consequence of early bipolar disorder [1607].

Below is a summary of the studies that 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 [1603]. The authors found that cannabis use at baseline was associated with follow-up mania (OR = 5.32, 95% CI = 3.59, 7.89). After adjusting for confounding factors, the association persisted, although it was reduced (OR = 2.70, 95% CI = 1.54, 4.75). The risk of developing manic symptoms appeared to increase with increased baseline frequency of cannabis use. The effect size was largest for those who used cannabis three to four days per week, followed by those who used daily and one to two days per week, and lastly for those who used one to three days per month. The authors reported that manic symptoms at baseline did not predict cannabis use during follow-up. The authors concluded that cannabis use increased the risk of developing subsequent manic symptoms and that this effect was dose-dependent.

Another group of investigators conducted a five-year, prospective, cohort study examining three groups of patients: one where a CUD preceded the onset of bipolar disorder, another where bipolar disorder preceded a CUD, and one group with bipolar disorder only [1604]. 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.

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 cannabis abuse preceded or coincided with, but did not follow, exacerbations of affective illness [1610].

A two-year, prospective, observational study on the outcome of pharmacological treatment of mania (the **E**uropean **M**ania in **B**ipolar **L**ongitudinal **E**valuation of **M**edication study, **EMBLEM**) 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 [193]. The study concluded that during a one-year treatment period, patients using cannabis exhibited less treatment compliance and higher levels of overall illness severity, mania, and psychosis compared to non-users. Patients using cannabis also reported experiencing less satisfaction with life.

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 [1606]. Genetic studies have also raised the possibility of a link between allelic variants of the cannabinoid receptor gene (*CNR1*) and susceptibility to mood disorders [1611, 1612].

The influence of cannabis use on age at onset of both schizophrenia and bipolar disorder (with psychotic symptoms) has been studied using regression analysis [186]. 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 younger age at onset of both disorders. 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. In bipolar patients, cannabis use reduced age at onset by an average of nine years. In contrast, in schizophrenic patients, cannabis use reduced age at onset by an average of 1.5 years. No significant difference was noted in age at onset between male and female patients in either of the diagnostic groups.

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 [1613]. 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 [1605]. 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.

One study reported that when compared with controls, patients with bipolar disorder were almost seven times (95% CI = 5.41 – 8.52) more likely to report a lifetime history of cannabis use [1605]. 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). Furthermore, those who used cannabis prior to the onset of a bipolar disease episode were 1.75 times (95% CI = 1.05 – 2.91) more likely to report disability attributable to bipolar disorder.

On the other hand, a retrospective analysis of a large cohort of bipolar I subjects, with or without a history of a CUD, reported that bipolar patients with a CUD had similar age at onset as patients without such a substance use disorder [1614]. However, patients with a CUD 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.

An epidemiological study using data from the 2001 – 2002 **NESARC** examined the relationship between bipolar disorder and CUD and reported that among approximately 2 000 individuals with a lifetime prevalence of bipolar disorder, the rates of CUD in the past 12 months were 7.2% (CI = 5.8 – 9.0) compared with 1.2% (CI = 1.1 – 1.3) in the general population [1602]. Furthermore, logistic regression analysis suggested that individuals with bipolar disorder and co-occurring CUD were at increased risk for nicotine dependence (AOR = 3.8), alcohol (AOR = 6.6) and drug (AOR = 11.9) use disorders as well as anti-social personality disorder (AOR = 2.8) compared to those without a CUD. Among individuals with bipolar disorder, the majority with CUD were male (62%) and young (18 – 29 years old) (70%). Furthermore, age-at-onset of bipolar disorder was earlier among individuals with co-occurring CUD, regardless of whether first episode was depressive or manic/hypomanic. No significant difference was found in lifetime rates of suicide attempts or suicidal ideation among individuals with and without a CUD. Among individuals with bipolar disorder and co-occurring CUD, 75% had a hypomanic, manic or depressive episode in the past 12 months. CUD was also associated with poorer physical QoL (i.e. arteriosclerosis). Limitations of the study included self-report methodology, lack of semi-structured interviews conducted by mental health professionals, and exclusion of the adolescent population that is most at-risk.

A cross-sectional observational study of 324 patients with bipolar disorder diagnosed through structured diagnostic interviews found evidence for a dose-response relationship between cannabis use and age at onset in bipolar disorder, which remained statistically significant after controlling for possible confounders (i.e. gender, family history, tobacco smoking, alcohol consumption, and other substance use disorders). However, the authors did not find an association between cannabis use and presenting polarity or presence of psychosis [1615]. The findings show a decrease in age at onset of approximately three years in those who reported using cannabis > 10 times per month compared to never users or those who reported using < 10 times per month. Furthermore, those patients with a lifetime CUD (i.e. abuse or dependence) had the greatest decrease in age at onset of approximately five years compared to never users or those who used < 10 times per month. Patients with a depressive presenting polarity had a lower age at onset compared to those with (hypo) manic/mixed or mixed onsets, while age at onset decreased as level of cannabis use increased. The authors concluded that there is evidence for a dose-response relationship between cannabis use and earlier onset of bipolar disorder. They also suggest that there is a tendency for onset of bipolar disorder to be preceded by cannabis use suggesting that cannabis use may be a risk factor for precipitating bipolar disorder.

A three-year prospective follow-up survey exploring the association between cannabis use, major depressive disorder and bipolar disorder from the 2001 – 2002 **NESARC** found a crude association between weekly (i.e. 2.25 days of use per week and 1.88 joints per day) and daily/almost daily (i.e. 6.45 days of cannabis use per week and 3.45 joints per day) cannabis use and bipolar disorder [1616]. However, this association no longer persisted after adjustment for confounding factors. The authors suggest that association between cannabis use and bipolar syndrome may be mediated by additional factors such as psychiatric and substance use disorders.

EMBLEM, a two-year prospective observational study in adults with manic/mixed episode of bipolar disorder, found that of 1 922 patients analyzed, previous cannabis users had the highest rates of remission (68.1%) and recovery (38.7%) and the lowest rates of recurrence (42.1%) and relapse (29.8%) [1617]. In contrast, current users had lower recovery and remission, higher recurrence, greater work impairment, and were more likely not to be living with a partner than never users. In addition, current cannabis users had a significantly higher rate of suicide attempts over the two-year follow-up compared with past and never users. These findings led the authors to conclude that bipolar patients who stop using cannabis during a manic/mixed episode have similar clinical and functional outcomes at two years compared to those who have never used cannabis, whereas patients who continue to use cannabis have a higher risk of recurrence and poorer functioning.

A study using experience sampling methodology (ESM), through diary entries, to track the temporal associations over a period of six days between cannabis, affect and bipolar disorder symptoms among 24 participants diagnosed with bipolar disorder type I or type II found that higher levels of positive affect increased the odds of using cannabis (OR = 1.25, CI = 1.06 – 1.47) and cannabis use was associated with subsequent increases in positive affect (but not negative affect), manic symptoms, and depressive symptoms [1608]. On the other hand, neither negative affect, manic, nor depressive symptoms predicted the use of cannabis. The average number of joints used per day was 2.5, with the majority (54%) of respondents reporting using skunk-type (i.e. high potency) cannabis. The authors suggest that individuals with bipolar disorder are not using cannabis to self-medicate minor fluctuations in negative affect and bipolar symptoms. Limitations of the study include small sample size, self-report, lack of more granular information on cannabis potency, and limited evidence for validity of scales for mania and depression designed for the ESM study. The authors of the study emphasize that while some individuals perceive cannabis as a useful coping strategy in the management of bipolar disorder symptoms, the results of the study suggest cannabis is not being used to self-medicate changes in symptoms in the context of daily life and may actually be further complicating affective states.

A 24-month prospective, naturalistic, observational study using data gathered under the **B**ipolar **C**omprehensive **O**utcomes **S**tudy (**BCOS**) examined the impact of cannabis use in 239 patients with bipolar disorder type I and schizoaffective disorder-bipolar type and found that cannabis use was significantly associated with decreased likelihood of remission during the 24-month follow-up period [1618]. Subgroup analyses reported that cannabis use was significantly associated with lower remission rates on the Hamilton Depression Rating Scale in females and patients who were prescribed mood stabilizers. On the other hand, in males and patients prescribed olanzapine and/or a mood stabilizer, cannabis use was significantly associated with lower remission rates on the Young Mania Rating Scale. Remission rates appeared lowest in the group reporting concurrent cannabis and tobacco use, followed by the group reporting smoking only tobacco and the non-smoker group. Overall, the study authors suggest that cannabis use is associated with decreased likelihood of long-term remission in bipolar spectrum disorders with particular interaction effects of cannabis use and mood symptoms on gender and medication type.

An epidemiological study providing the first nationally representative information on the prevalence and correlates of DSM-5 CUD using data from the 2012 – 2013 wave of the **NESARC-III** reported that past-year CUD was associated with bipolar I disorder (AOR = 5.0) and lifetime CUD was also associated with bipolar I disorder (AOR = 3.8); past-year CUD was also associated with bipolar II disorder (AOR = 2.7) and lifetime CUD was also associated with bipolar II disorder (AOR = 2.8) [338]. Furthermore, only the association between bipolar I and past-year CUD increased with increasing severity of CUD (AOR = 3.4, 4.1, and 10.1 for mild, moderate, and severe CUD respectively).

A review article examining the state of the evidence regarding the use of cannabis as a predictor of early onset of bipolar disorder and suicide attempts reported that cannabis use, in patients with bipolar disorder, is associated with increased risk of suicide attempts and with early age at onset of the disorder (reduced by between six and nine years) [1619]. Early age at onset is associated with greater number of rapid cycling episodes, mixed episodes, psychotic episodes, panic disorder, anxiety disorder, substance use disorder, major depression, worse response to lithium and suicidal behaviour. Limitations of the review article include the sparse literature on cannabis use, early age at onset of bipolar disorder and suicide attempts; the variable definition of early age at onset among the included studies; and methodological and other differences between the studies.

A recent systematic review of 12 cohort studies (2 588 individuals 'more exposed' to cannabis/9 371 'less exposed to cannabis') examined the longitudinal association between cannabis use and symptomatic outcomes among individuals living with a baseline anxiety or mood disorder. Relative to those less exposed to cannabis (including abstainers), the review provided consistent evidence that 'recent' cannabis use (within the last 6 months) was associated with negative symptomatic outcomes over time with respect to PTSD, panic disorder, bipolar disorder, and depressive disorder. Specifically, those using cannabis were more likely to report persistent symptoms over time and less likely to improve symptomatically from treatment (i.e., medication and/or psychotherapy). Some evidence further supported that reducing/stopping use was associated with more favourable outcomes. Overall, the study suggested that the available evidence does not support that cannabis can help long-term symptoms associated with anxiety and mood disorders, but rather, cannabis use may sustain symptoms longitudinally and prevent recovery efforts. However, the authors note that the findings should be interpreted with caution, considering the observational designs across studies (causality not established) and the biases associated with the samples (e.g., inpatients) and sources of cannabis consumed (i.e., unregulated sources with likely higher THC and minimal CBD concentrations) [1620].

7.7.3.2 Schizophrenia and psychosis

- ***Evidence from clinical studies suggests that acute exposure to (THC-predominant) cannabis or THC is associated with dose-dependent, acute and transient behavioural and cognitive effects mimicking acute psychosis.***
- ***Epidemiological studies suggest an association between (THC-predominant) cannabis use, especially early, chronic,and heavy use and psychosis and schizophrenia.***
- ***The risk of schizophrenia associated with cannabis use is especially high in individuals who have a personal or family history of schizophrenia.***
- ***Cannabis use is also associated with earlier onset of schizophrenia in vulnerable individuals and exacerbation of existing schizophrenic symptoms and worse clinical outcomes.***

Acute psychotic reactions

THC-predominant cannabis and psychoactive cannabinoid (e.g. THC, nabilone, dronabinol, nabiximols) use have been linked to episodes of acute psychosis in both regular and drug-naïve users [145, 182, 183, 200, 205, 541, 1085, 1621].

A clinical experimental study that involved intravenous administration of THC (paralleling peak blood levels of THC achieved non-medically by smoking) to healthy volunteers without a history of psychiatric disorders or current concomitant drug use showed that THC administration was associated with a variety of acute, transient behavioural and cognitive effects typically associated with an acute psychotic reaction [201]. These effects included 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.

Schizophrenia and psychosis

Schizophrenia is a chronic and devastating mental disorder that typically presents in late adolescence/early adulthood [1084]. Although the incidence of schizophrenia is relatively low at 10 – 22 per 100 000, its prevalence is relatively high (0.3 – 0.7 per 100) because of its chronic nature [1084].

Increasing evidence suggests an important role for the ECS in the pathophysiology of schizophrenia and psychosis [177, 1084, 1085] and also see **Section 4.9.5.5** for more information. In addition, there is consensus across studies of a robust association between cannabis use and schizophrenia/psychosis. For example, a number of studies report that rates of cannabis use seem to be about twice as high among patients with psychosis than among controls [1622]. Furthermore, cannabis (and THC) has been shown to produce a full range of positive symptoms (e.g. suspiciousness, paranoid and grandiose delusions, hallucinations, conceptual disorganization, fragmented thinking, and perceptual alterations), negative symptoms (e.g. blunted affect, emotional withdrawal, psychomotor retardation, lack of spontaneity, and reduced rapport), and cognitive impairments (e.g. deficits in verbal learning, short-term memory, working memory, executive function, abstract ability, decision making, attention, and time perception abnormalities) in healthy volunteers that closely resemble the classical symptoms of schizophrenia [183, 1085].

The association between cannabis and psychosis fulfills many, but not all, of the standard criteria for causality such as temporal relationship, biological gradient, biological plausibility, coherence, consistency, and experimental evidence [183, 1085]. Furthermore, cannabis appears to be neither necessary nor sufficient to cause a persistent psychotic disorder such as schizophrenia [183, 1085]. Rather, it appears that cannabis use is but a component cause that can, in concert with known and unknown factors, contribute to the overall risk of schizophrenia [183, 1085]. For example, the link between cannabis and psychosis is moderated by factors such as age at onset of cannabis use, childhood abuse, and genetic vulnerability [183].

The weight of the evidence suggests the association between cannabis exposure and schizophrenia is modest but consistent [183]. Furthermore, the bulk of the literature suggests that individuals with a family history of schizophrenia, individuals with prodromal symptoms, and individuals who have experienced discreet episodes of psychosis related to cannabis should be strongly discouraged from using (THC-predominant) cannabis and psychoactive cannabinoids [183].

The following sections summarize some of the more salient literature regarding the association between cannabis use and schizophrenia and psychosis. Of note, the majority of studies have focused on cannabis use and positive symptoms, with far less attention being paid to the association between cannabis use and negative symptoms and cognitive deficits in schizophrenia [183].

A 15-year, prospective, longitudinal cohort study of over 45 000 male Swedish conscripts examining the association between cannabis use and risk of schizophrenia reported that the relative risk of schizophrenia among high consumers of cannabis (> 50 lifetime occasions) was 6.0 (95% CI = 4.0 – 8.9) compared with non-users [203]. The relative risk was 2.4 among the individuals that reported use of cannabis at least once compared with non-users (95% CI = 1.8 – 3.3). Furthermore, the relative risk was dose-dependent, increasing with increasing consumption level. Aside from cannabis consumption, diagnosis of other psychiatric disease other than schizophrenia at conscription, disturbed conditions of upbringing, solvent abuse and poor adjustment in school were all strongly associated with increased occurrence of schizophrenia. Adjustment for other confounders weakened the association between cannabis use and risk of schizophrenia, though the association persisted and was still statistically significant.

A three-year, prospective, longitudinal, population-based study of the prevalence, incidence, course and consequences of psychiatric disorders in the Dutch general population (**NEMESIS**) reported that baseline history of cannabis use increased the risk of a follow-up psychosis outcome for subjects with a lifetime absence of psychosis (AOR = 2.76, 95% CI = 1.18 – 6.47) as well as increased the risk of severe level of psychotic symptoms (OR = 24.17, 95% CI = 5.44 – 107.46) [202]. In addition, there was a dose-response relation between exposure load and psychosis outcome. A strong additive interaction was found between cannabis use and established vulnerability to psychotic disorder (risk difference 54.7%) compared to those without an established vulnerability (risk difference 2.2%).

In a historical cohort study of over 50 000 male Swedish conscripts, self-reported use of cannabis in adolescence was associated with an increased risk of developing schizophrenia, and this risk was related to frequency of cannabis exposure (i.e. was dose-dependent according to frequency of use) [1623]. The AOR for lifetime cannabis use greater than 50 times was 6.7 among the group of individuals that reported using only cannabis.

The Dunedin Multidisciplinary Health and Development Study was a longitudinal, prospective cohort study of over 1 000 individuals followed from birth to age 26 that, among other goals, evaluated the effects of cannabis use on mental health outcomes [1624]. The study evaluated the psychiatric health of individuals before drug use typically begins (at age 11) as well as at age 26, and also obtained information about drug use at ages 15 and 18 from individual self-reports. Linear regression analyses showed that individuals reporting cannabis use by age 15 and 18 had significantly more schizophrenia symptoms than controls at age 26, even after controlling for psychotic symptoms at age 11. Furthermore, the study reported that individuals who used cannabis at age 15, but not age 18, were more than four times as likely to have a diagnosis of schizophreniform disorder at age 26 than controls, however this effect was no longer significant after controlling for psychotic symptoms at age 11. Cannabis use by age 15 did not however predict depressive outcomes (i.e. depressive symptoms or depressive disorder) at age 26. The authors concluded that cannabis exposure among psychologically vulnerable adolescents, especially by age 15, should be strongly discouraged.

A review of five epidemiological studies [202, 203, 1623-1625] by Arseneault et al. (2004) indicated that cannabis appears to be neither necessary nor sufficient to cause psychosis or schizophrenia but rather that it is only one factor in a larger constellation of contributing factors [1622]. On an individual level, cannabis use confers an overall two-fold increase in the relative risk for later schizophrenia (AOR = 2.34, CI 95% = 1.69 – 2.95), while at a population level, elimination of cannabis use would reduce the incidence of schizophrenia by approximately 8%, assuming the relationship is truly causal [1622].

A population-based, first-contact incidence study conducted in the Netherlands with 133 patients assessing the independent influences of gender and cannabis use on milestones of early course in schizophrenia reported that male patients were significantly younger than female patients at first social and/or occupational dysfunction, first psychotic episode, and first negative symptoms [1519]. Cannabis-using patients were also significantly younger at these milestones than patients who did not use cannabis. Further analysis showed that cannabis use, but not gender, made an independent contribution to the prediction of age at first psychotic episode with male cannabis users on average almost seven years younger at onset of illness than male non-users.

The relationship between cannabis use and psychotic symptoms was also studied in a prospective 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 [198]. The study was part of the **E**arly **D**evelopmental **S**tages of **P**sychopathology (**EDSP**) study in which data were collected on the prevalence, incidence, risk factors, comorbidity, and four-year course of mental disorders in a random regional representative population sample of adolescents and young adults. After adjustment for confounding factors, cannabis use at baseline was associated with an increase in the cumulative incidence of psychotic symptoms at follow-up four years later (AOR = 1.67, 95% CI = 1.13 – 2.46). The effect of cannabis use was much stronger in those individuals with any predisposition for psychosis at baseline (24% adjusted difference in risk, 95% CI = 7.9 – 39.7, $p = 0.003$) compared to those without (5.6%, 95% CI = 0.4 – 10.8, $p = 0.003$). The authors also found a dose-response relationship between frequency of cannabis use and the risk of psychosis. Near daily use of cannabis at baseline was associated with an AOR of more than 2 for any psychotic symptoms, while cannabis use less than once per month carried the same risk as no cannabis use. Lastly, predisposition for psychosis at baseline did not significantly predict cannabis use four years later (AOR = 1.42, 95% CI = 0.88 – 2.31). The authors conclude that any cannabis use at baseline moderately increases the risk of psychotic symptoms in young people but those individuals with a predisposition to psychosis have a far greater risk of developing psychotic symptoms as a result of cannabis use.

A 25-year longitudinal study of the health, development, and adjustment of a birth cohort of 1 265 New Zealand children (i.e. The Christchurch Health and Development Study) examining the association between cannabis use and mental health outcomes reported that daily users of cannabis had rates of psychotic symptoms that were between 1.6 and 1.8 times ($p < 0.001$) higher than non-users of cannabis [1626]. Regression models indicated that cannabis use had a positive and significant effect on psychotic symptoms suggesting that increasing cannabis use was associated with increased symptom levels. Furthermore, according to the authors, the data suggest that it was unlikely that the development of psychotic symptoms led to increased cannabis use.

A systematic review and meta-analysis of population-based longitudinal studies or case-control studies, nested within longitudinal designs, that examined cannabis use and the risk 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 (pooled AOR = 1.41, 95% CI = 1.20 – 1.65) [196]. This translated into an increase in risk of psychosis of about 40% in participants who had ever used cannabis. Furthermore, the findings appeared to show a dose-related effect, with greater risk to individuals who used cannabis most frequently (OR = 2.09, 95% CI = 1.54 – 2.84) [186, 192, 196].

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 [192]. The study concluded that lifetime cannabis abuse/dependence was associated with a significantly earlier age at onset of psychosis (3.1 years, 95% CI = 1.4 – 4.8). 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. 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.

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 [186]. 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. 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. In bipolar patients, cannabis use reduced age at onset of bipolar disorder by an average of nine years. In contrast, in schizophrenic patients, cannabis use reduced age at onset by an average of 1.5 years. No significant difference was noted in age at onset between male and female patients in either of the diagnostic groups.

A 35-year follow-up cohort study of 50 087 Swedish military conscripts examining the association between cannabis use and mental health outcomes found that the OR for psychotic outcomes among frequent cannabis users compared with non-users was 3.7 (95% CI = 2.3 – 5.8) for schizophrenia, 2.2 (95% CI = 1.0 – 4.7) for brief psychosis, and 2.0 (95% CI = 0.8 – 4.7) for other non-affective psychoses [1627]. Furthermore, the risk of schizophrenia declined over the decades in moderate users but much less so in frequent users. Thus, the authors found a dose-dependent association between cannabis use and risk of schizophrenia. In addition, the presence of a brief psychosis did not increase the risk of later schizophrenia in cannabis users compared with those who did not use. According to the study authors, this suggested that cannabis does not seem to play a major role in the transition from brief psychotic episodes to schizophrenia. One of the main limitations of the Swedish conscript study was that data regarding use of cannabis was limited to the period before conscription.

A preliminary study that evaluated the effects of cannabis use on neurocognitive functions in 28 schizophrenia outpatients who met DSM-IV criteria for schizophrenia (age 18 – 45) reported a deficit in sustained attention and increased impulsivity in schizophrenia patients reporting heavy cannabis use [1628]. However, it also appeared that heavy cannabis-using subjects generally had a higher level of functioning and did not differ from non-cannabis using schizophrenia patients in other tested functions, raising the possibility of higher pre-morbid functioning among cannabis-using schizophrenia patients. Since this study was cross-sectional, it is not possible to determine the causal relationship between neurocognitive functioning and heavy cannabis use among schizophrenia patients.

In one case-control study with 280 people with a first episode of psychosis and 174 healthy controls, patients reported using higher-potency cannabis containing high amounts of THC (16% THC) and low amounts of CBD ("skunk-like" cannabis) compared to the controls who reported using cannabis containing equal amounts of THC and CBD [1112]. Furthermore, daily use of "skunk-like" cannabis was associated with an earlier age of onset of psychosis compared to non-cannabis users [1113]. In a follow-up case-cohort study by the same group of 410 patients with first-episode psychosis and 370 population controls, daily use of "skunk-like" cannabis was associated with a more than five-fold increased risk of first-episode psychosis, whereas use of "skunk-like" cannabis on weekends was associated with a nearly three-fold increased risk of first-episode psychosis [173]. By contrast, the OR of a first-episode psychosis associated with the use of "skunk-like" cannabis less than once per week, use of hash every day, on weekends, and less than once per week was not statistically significant compared with never use of cannabis [173].

A prospective, population-based birth cohort study of 1 756 adolescents (**ALSPAC**) examined the relationship between cannabis, tobacco, and psychotic experiences [1629]. First, cigarette and cannabis use at age 16 were highly correlated. Next, cannabis use and cigarette use at age 16 were both associated, to a similar degree, with psychotic experiences at age 18 (OR = 1.48, 95% CI = 1.18 – 1.86; or alternatively a 3.2 fold increase in odds of psychotic experiences for those who used cannabis > 60 times). For cigarettes, the OR was 1.61 (95% CI = 1.31 – 1.98; or a 4.2-fold increase in odds in daily smokers vs. non-smokers). Adjustment for cigarette smoking frequency (AOR = 1.27, 95% CI = 0.91 – 1.76; or a 1.2-fold increase in risk in those who used cannabis most heavily compared to never users) or other illicit drug use (AOR = 1.25, 95% CI = 0.91 – 1.73), substantially attenuated the relationship between cannabis and psychotic experiences. The degree of attenuation was less when cannabis use was adjusted for in the cigarette-psychotic experience association (OR = 1.42, 95% CI = 1.05 – 1.92; or a 2.9-fold increase in risk in daily smokers compared to non-smokers). The study authors suggest that measurement of the risk of psychotic experiences associated with cannabis exposure is sensitive to confounding factors such as cigarette smoking, a behaviour which is highly correlated with cannabis use and which is difficult to tease out from cannabis use.

A longitudinal, case-control study in Sweden investigated the causal nature of the association between cannabis abuse and a future diagnosis of schizophrenia reported that within the general Swedish population, cannabis abuse was strongly associated with later schizophrenia (OR = 10.44, 95% CI = 8.99 – 12.11) [1630]. The association was substantially attenuated both by increasing temporal delay between cannabis abuse exposure and schizophrenia diagnosis and by controlling for increasing degrees of familial confounding. Fully controlling for familial confounders reduced the association between cannabis abuse and later schizophrenia (OR = 3.3 and 1.6 with three- and seven-year temporal delays respectively). Of note, opiate, sedative, cocaine/stimulant and hallucinogen abuse were also strongly associated with subsequent schizophrenia in the general population. Importantly, the authors of the study suggest that a large part of the cannabis abuse and schizophrenia association observed in the general population is not causal and results from confounding due to shared familial factors. Thus, shared genetic risk factors contribute substantially to the cannabis abuse and schizophrenia association. The authors also note that familial environmental factors also influence the co-occurrence of cannabis abuse and schizophrenia. Nonetheless, the authors of the study suggest that the findings of the study continue to support the hypothesis that cannabis abuse of sufficient severity has a significant causal impact on future risk for schizophrenia. Thus, it seems that risk of schizophrenia is subject to a number of influences including genetic predisposition, familial environment and severity of cannabis abuse.

A systematic review and meta-analysis of the literature investigating the association between the extent of cannabis consumption and psychosis-related outcomes found that higher levels of cannabis use were associated with increased risk for psychosis with an OR = 3.90 (95% CI = 2.84 – 5.34) for the risk of schizophrenia and other psychosis-related outcomes among the heaviest cannabis users compared to non-users [1368].

An on-line, prospective study that recruited slightly more than 700 participants with the goal of investigating the existence of a longitudinal relationship between change in cannabis use and psychotic experiences reported that a reduction in cannabis use was associated with a reduced frequency of psychotic experiences at follow-up (β = -0.096, p = 0.01) [1631]. On the other hand, an increase in cannabis use was not significantly associated with the number of psychotic experiences at follow-up. While the decrease in cannabis use was associated with fewer positive symptoms at follow-up in the unadjusted model (β = -0.12, p = 0.002), this was not the case in the adjusted model (β = -0.06, p = 0.06). An increase in cannabis use was associated with a higher score in the community assessment of psychic experiences (CAPE) subscale of measures of positive symptoms (β = 0.07, p = 0.02) in the fully adjusted model, while no significant association was found between change in cannabis use and the "Negative" subscale. A decrease in cannabis use was predictive of a lower score at follow-up on the "Depressive" subscale but only in the unadjusted model. Given the findings, the authors suggest that cessation of cannabis use may be beneficial in reducing the risk of clinical psychosis, and especially the risk of positive symptoms, in the long term.

A recent systematic review and meta-analysis, that included 24 studies and over 16 000 participants, showed that independent of stage of illness, continued cannabis use in patients with a pre-existing psychotic disorder was associated with a greater increase in relapse of psychosis compared to patients who never used or discontinued use [164]. Continued use was also associated with longer hospital admissions. Furthermore, there was a greater effect of continued use over discontinued use on relapse, positive symptoms, and level of functioning, but not on negative symptoms.

A subsequent observational study of 256 patients, 18 – 65 years of age, with first-episode psychosis showed that former regular users of cannabis who stopped using after the onset of psychosis had the most favourable illness course with regards to relapse, whereas continued high-frequency use (i.e. daily use) of high potency ("skunk-like") cannabis was associated with the worst outcome [165]. High-frequency, high-potency users had an OR = 3.28 (95% CI = 1.22 – 9.18) of a subsequent relapse, an OR = 1.77 (95% CI = 0.96 – 3.25) of more relapses, and an OR = 3.16 (95% CI = 1.26 – 8.09) of more intense psychiatric care after onset of psychosis as well as fewer months until a relapse occurred.

Another recent prospective cohort study of 220 patients with first-episode psychosis, 18 – 65 years of age, reported that there was an increase in the odds of experiencing a relapse of psychosis during periods of cannabis use relative to periods of no use (OR = 1.13; 95% CI = 1.03 – 2.24) [166]. The authors suggest that it is more likely than not that continued cannabis use after onset of psychosis is causally, and dose-dependently, associated with increased risk of relapse of psychosis resulting in psychiatric hospitalization.

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 *COMT* gene locus [1116-1120], while others have focused on polymorphisms at the *AKT1* gene locus [1124-1127], the *BDNF* gene [1632], the *DAT1* gene or the *CNR1* gene loci [1633-1635].

Schizophrenia and the COMT gene

COMT regulates the breakdown of catecholamines, including neurotransmitters such as dopamine, epinephrine, and norepinephrine [1120]. 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 [1636, 1637]. Changes in dopaminergic tone and signaling are known to affect neurophysiological function, and these changes have been implicated in the pathophysiology of schizophrenia [1638]. Although an earlier large-scale association study and meta-analysis failed to find a strong association between the Val158Met *COMT* polymorphism and vulnerability to schizophrenia [1639], later studies (below) appear to suggest an association.

Caspi et al. [1116] 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. Subsequent studies confirmed and extended these findings [1117-1120, 1126]. 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 [1117]. 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 [1118]. 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 [1118].

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 [1119]. 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 [1120]. 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 [1120]. In addition, evidence gathered from convergent functional genomic data implicates the *COMT* gene (as well as the *CNR1* and *2* genes) in the pathophysiology of schizophrenia [1640].

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, in regulating cellular metabolism, cell stress, cell-cycle regulation, and apoptosis as well as regulating neuronal cell size and survival [1124]. In one study, the authors found evidence of a gene-environment interaction between a SNP in the *AKT1* gene (rs2494732, C/C homozygous polymorphism) and cannabis use [1125]. 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 [1125]. 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 [1125]. 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 [1124]. A naturalistic study of 442 healthy, young cannabis users (308 males and 114 females) between 16 and 23 years of age examined associations between variations at the *AKT1* gene locus and acute psychotic symptoms and cognitive function and level of THC in subjects' own cannabis [1127]. The study found that variation at the *AKT1* gene locus predicted acute psychotic response to cannabis along with cannabis dependence and baseline schizotypal symptoms. Furthermore, the study found that working memory following acute cannabis exposure was poorer in females compared to males.

Schizophrenia and the BDNF 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 hospital admission by almost three years [1632]. 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. 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. In this 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 *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.

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 that includes a psychiatric history/evaluation, would be very valuable in determining whether cannabis/cannabinoids represent a sensible and viable therapeutic option.

A population-based study evaluated whether the association between cannabis use (by 16 years of age) and cortical maturation in adolescents is moderated by a polygenic risk score for schizophrenia [1110]. In this study, three different population groups were examined: 1 024 adolescents of both sexes from the Canadian **S**aguenay **Y**outh **S**tudy (**SYS**), 426 adolescents of both sexes from the **IMAGEN** study, and 504 male youth from the **ALSPAC** study. In total, 1 577 participants (aged 12 – 21 years) were studied. The findings of the study suggest a negative association between cannabis use in early adolescence and cortical thickness in male participants with a high polygenic risk score for schizophrenia. In the **SYS** and **IMAGEN** groups, higher risk scores were associated with a lower cortical thickness only in males who used cannabis. In the **ALSPAC** group, those individuals who used cannabis most frequently (≥ 61 occasions) had lower cortical thickness compared to those who never used cannabis and those with light use. The authors concluded that cannabis use in early adolescence moderates the association between the genetic risk for schizophrenia and cortical maturation among male individuals. Furthermore, the authors suggest that cannabis use might interfere with the maturation of the cerebral cortex in male adolescents at high risk for schizophrenia. Cannabis exposure may further accelerate the natural course of cortical thinning in male adolescents with a high polygenic risk score.

Identification of groups at high-risk

A number of studies have sought to identify subgroups of individuals who may be at particularly high risk of developing psychosis and schizophrenia associated with cannabis use [1109]. Age of use, genetic susceptibility, family history, childhood trauma and strains of cannabis were all examined in a review by Gage et al. (2015) [1109]. Regarding age of use, the evidence suggests that earlier onset of cannabis use is associated with an increased risk of psychosis, schizophreniform disorder, or schizophrenia although it is not fully clear at the moment whether this is the result of a specific "window of vulnerability" in adolescence or rather the result of a longer period of cumulative use (i.e. those individuals who began using cannabis at an earlier age may have used cannabis on more occasions by the time the outcome measure was evaluated) or even a function of other confounding factors such as history of abuse or family socio-economic level [1085, 1109, 1111].

A recent 15-year longitudinal study of 6 534 adolescents from Finland suggested that cannabis use was associated with an increased risk in developing psychosis by age 30. The survey-based data found that individuals who tried cannabis at least five times or more were at the highest risk (HR = 6.5, 95% CI = 3.0-13.9) of developing psychosis 15 years later, even after controlling for prodromal symptoms, poly-substance use, and parental psychosis [1641].

A recent 4-year longitudinal study monitoring individual-level data from 3720 Canadian adolescents found that 'frequent' (daily/near daily) cannabis use at baseline (age 13) predicted self-reported psychotic symptoms one year later (age 14). Participants completed an annual web-based survey for four years from age 13 to 16. In the subsequent time-point assessments following baseline, cannabis use predicted psychotic symptoms that year and one year later. For example, cannabis use at age 14 predicted psychotic symptoms at age 14 and one year later (age 15); cannabis use at age 15 predicted psychotic symptoms at age 15 and one year later (age 16). The overall findings imply that using cannabis often during the early teenage years may increase the risk in the development and persistence of psychotic symptoms. Key limitations in this study relate to the associative findings (causality not established) and not accounting for family history of psychosis in analyses [1642].

Regarding genetic susceptibility, a number of studies suggest an important role for a number of different genes in modulating the susceptibility to psychotic disorders in those who use cannabis (*COMT*, *AKT1*, *BDNF*, *DAT1*, *NRG1*, *CNR1* and see previous section). While the evidence regarding the influence of the *COMT* gene has been called into question, other genes (*AKT1*, *BDNF*, *DAT1*, *NRG1*, *CNR1*) may still contribute to the risk of developing psychotic disorders associated with cannabis use [1085, 1109, 1111].

A few studies have found that childhood trauma when combined with cannabis use increases the absolute risk of psychosis to a greater degree than the sum of either risk factor alone [1085, 1109, 1111]. ORs of developing psychosis in adolescence where there is a history of abuse or trauma have been reported to be between 11.96 (95% CI = 2.10 – 68.22) and 20.9 (95% CI = 2.3 – 173.5) [1085].

A positive family history of schizophrenia has also been linked to an increased risk of experiencing cannabis-induced psychotic disorders [1085]. For example, one population-based cohort study of 2 276 309 individuals that sought to establish the rate ratios of cannabis-induced psychosis associated with predisposition to psychosis and other psychiatric disorders in a first-degree relative and compare them with the corresponding rate ratios for developing schizophrenia spectrum disorders reported that children with a mother with schizophrenia had a five-fold increased risk of developing schizophrenia and a 2.5-fold increased risk of developing cannabis-induced psychosis [1643].

Lastly, a number of studies have examined the association between use of different strains of cannabis and risk of psychosis [1085, 1109, 1111]. Overall, the findings appear to suggest that strains with a higher THC to CBD content are associated with an increased risk of psychosis, although additional research is required to further substantiate these findings [1109].

7.7.3.3 Suicidal ideation, attempts and mortality

- ***Evidence from epidemiological studies also suggests a dose-dependent effect between cannabis use and suicidality, especially in men.***

Evidence from epidemiological studies suggests suicidal thoughts and behaviours (ideation, planning, attempt) are strongly related to substance use behaviours, including cannabis use [178]. A number of epidemiological studies have found a statistically significant association between cannabis use, especially cannabis use that begins early and that is heavy (i.e. daily) and suicidality [168, 169, 178, 1644]. While the precise mechanism of action linking cannabis use, especially heavy use, with an increased risk of suicidality is not clear, evidence from clinical studies with rimonabant, a CB_1 receptor antagonist, showed that rimonabant use was statistically significantly associated with an increased risk of suicidal ideation and attempt (OR = 1.9, 95% CI = 1.1 – 3.1) [1645, 1646]. Together, findings from epidemiological studies and clinical studies with rimonabant raise the possibility that downregulation of CB_1 receptors achieved either through frequent heavy cannabis use (of THC-predominant/enriched cannabis) or administration of a CB_1 receptor antagonist (e.g. rimonabant) may potentially trigger suicidality, especially in susceptible individuals.

One 30-year longitudinal cohort study (Christchurch Health and Development Study) of 1 265 children reported that, after controlling for personal and family characteristics, there remained a statistically significant correlation between suicidal ideation and at least monthly cannabis use [1644]. In this study, regular cannabis use (i.e. at least several times per week to daily use) was estimated to significantly increase the risks of transitioning into suicidal thoughts for susceptible males but not females. Importantly, the study did not find a significant effect of suicidal ideation on the uptake of regular cannabis use (i.e. no reverse-causality).

A study using two community-based twin samples from the Australian Twin Registry composed of 9 583 individuals reported that all levels of cannabis use were associated with suicidal ideation, regardless of duration of use (OR = 1.28 – 2.00, $p < 0.01$) [178]. Cannabis use and endorsement of at least three symptoms were associated with unplanned (OR = 1.95 and 2.51 respectively, $p < 0.05$) but not planned, suicide attempts. Suicidal ideation, regardless of duration, showed a dose-dependent relationship with cannabis use, being more common in those reporting between three and six CUD symptoms (21 – 28%) compared to never users (6 – 12%), those with no symptoms (9 – 17%) and those with one to two CUD symptoms (13 – 21%). Importantly, associations persisted even after controlling for other psychiatric disorders and substance use. The study authors suggest the presence of overlapping genetic and environmental effects responsible for the co-variance between cannabis use and suicidal ideation.

A study using data drawn from waves 1 and 2 of **NESARC** reported that cannabis use was significantly associated with increased incidence of suicidality among men (AOR for any cannabis use = 1.91, 95% CI = 1.02 – 3.56), and particularly so with heavy use (i.e. daily/near-daily) (AOR = 4.28, 95% CI = 1.32 – 13.86), but not so among women [168]. Among women, baseline suicidality was associated with initiation of cannabis use among women (AOR = 2.34, 95% CI = 1.42 – 3.87), but not men. While the study reported a significant association between cannabis use and suicidal ideation, no association was found between cannabis use and suicide attempts.

A recent review and meta-analysis of the association between cannabis use and suicidality concluded that cannabis use, in particular heavy use (i.e. daily or near-daily) was associated with a modest effect on suicidality [169]. While the evidence of an association between *acute* cannabis use and imminent risk for suicidality was lacking, there was evidence to support that *chronic* cannabis use can predict suicidality. Pooled meta-analyses showed that any cannabis use was associated with increasing suicidal ideation (OR = 1.43, 95% CI = 1.13 – 1.83), and heavy cannabis use was associated with a higher risk of suicidal ideation (OR = 2.53, 95% CI = 1.00 – 6.39). Furthermore, pooled ORs estimate for any cannabis use and suicide attempt was 2.23 (95% CI = 1.24 – 4.00), and for any heavy cannabis use was 3.20 (95% CI = 1.72 – 5.94). Limitations of the meta-analysis include heterogeneity of the studies as well as publication bias.

7.7.3.4 Amotivational syndrome

- ***The available limited evidence for an association between cannabis use and an "amotivational syndrome" is mixed.***

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 [1647].

Some investigators suggest that heavy, chronic use of cannabis is linked to the development of such a syndrome [1647]; abstinence typically appears to result in resolution of symptoms [1365, 1648]. However, other investigators have not found such a causal relationship [1647, 1649]. There is some speculation that earlier studies may have been confounded by a number of variables such as other substance abuse, poverty, or other psychiatric disorders that could lend alternate explanations to the so-called "amotivational syndrome" [183].

8.0 Overdose/Toxicity

There has been no documented evidence of death exclusively attributable to cannabis overdose to date [1650], most likely because of the sparse expression of CB_1 receptors in the brainstem regions responsible for respiratory and cardiovascular control [771]. Using rodent LD_{50} values for oral administration, the equivalent lethal dose of THC in humans has been extrapolated to be >15 000 mg [1651, 1652]. Using a cannabis sample that contains 20% THC as an example, someone would need to orally ingest 75 000 mg of cannabis to reach this amount, which is greater than the amount of cannabis a very heavy user would use in a day (1 025 mg, range 652-1 336 mg, based on European data [1653]). The margin of exposure for THC is > 100 for individual exposure, population-based exposure calculated from prevalence data and population-based exposure calculated from sewage analysis [1654]. Nevertheless, a cannabis and THC overdose can produce dose-dependent unwanted and potentially significant mental and physical effects, typically dizziness, sedation, intoxication (euphoria), cognitive impairment, transient impairment of sensory and perceptual functions, clumsiness, dry mouth, hypotension, or increased heart rate [227, 1655]. These adverse effects are generally tolerable in healthy adults and not unlike those seen with other medications [140].

Acute psychological complications (e.g. panic attacks, severe anxiety, psychosis, paranoia, hallucinations, convulsions, hyperemesis etc.) that present to hospital Emergency Departments can be managed with conservative measures, such as reassurance in a quiet environment, and/or administration of benzodiazepines (5 to 10 mg diazepam p.o.) or i.v. fluids, if required [1656]. As is stated in the case of overdose with Marinol® [227], 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. The Marinol® monograph suggests that in the case of a serious recent oral ingestion, these should be managed with gut decontamination [227]. In unconscious patients with a secure airway, activated charcoal should be instilled (30 to 100 g in adults, 1 to 2 g/kg in infants) via a nasogastric tube [227]. A saline cathartic or sorbitol may be added to the first dose of activated charcoal [227].

Differences in pharmacokinetics and pharmacodynamics between different routes of administration such as smoking/vapourization and oral ingestion confer different overdose risks. Inhalation is typically associated with a large and rapid increase in blood cannabinoid levels while oral ingestion is associated with a smaller and slower increase in blood cannabinoid levels (see **Section 2.2.1** for more details). Consistent with these differences in pharmacokinetics, acute adverse effects associated with inhalation have a shorter onset of action as well as a shorter duration of action, while acute adverse effects associated with oral ingestion have a longer onset of action and a longer duration of action (see **Sections 2.2.1.1 – 2.2.1.4** for more details). The sudden spike in higher blood levels of cannabinoids associated with inhalation could lead to an acute overdose episode if self-titration is not properly employed; one study has shown while that cannabis users titrate their dose of THC by inhaling lower volumes of smoke when smoking "strong" joints, this did not fully compensate for the higher THC doses per joint when using "strong" cannabis and therefore users of more potent cannabis are exposed to greater quantities of THC [584]. On the other hand, the protracted onset of acute effects associated with oral ingestion can lead some individuals to consume more cannabis (and THC) than actually needed for a therapeutic effect in the belief that they have either not consumed enough or that an increased dose will lead to a faster onset of effects. These mistaken beliefs and actions could lead to an overdose. In one case series report from Colorado, five patients who were daily cannabis smokers and who reported using greater than 10 times the recommended dose of 10 mg of THC were admitted to psychiatric emergency services with edible cannabis-induced-psychosis [175]. Symptoms reported included labile disorganized thinking, poor insight and judgement, hyperreligious delusions, flat affect, grandiose delusions, auditory and visual hallucinations, combative and agitated behaviour, paranoia, euphoria, rapid speech, flight of ideas, suicidal ideation, insomnia, depressed mood. In all of the cases, psychosis resolved within one to two days with treatment and all patients returned to their baseline, normal mental state. No further psychiatric treatment was recommended at discharge. Two patients had one previous episode of inhaled cannabis-induced psychosis. In one case, family history was positive for schizophrenia and bipolar disorder but uncertain for the other patients. Treatment consisted of intramuscular haloperidol and/or lorazepam/midazolam, oral olanzapine, seclusion/restraint, or oral risperidone. In one case report, a 19-year old man who overdosed on an edible cannabis product (i.e. a cannabis cookie) began reportedly exhibiting erratic speech and hostile behaviours within the first 2.5 h following consumption and died from bodily trauma resulting from a jump from a balcony approximately 3.5 h following consumption of the edible [174].

THC

LD_{50} values for rats administered single oral doses of THC, or crude cannabis extract, are approximately 1 000 mg/kg [1657]. Dogs and monkeys are able to tolerate significantly higher oral doses of THC, or cannabis extract, of 3 000 mg/kg (or greater in certain cases) [1657]. The estimated human lethal dose of intravenous THC is 30 mg/kg (2 100 mg/70 kg) [227]. Conversion of this dose to an average inhaled or oral dose suggests an average inhaled dose of 7 350 mg THC (range: 6 300 mg to 8 400 mg/70 kg) and an average oral dose of 31 500 mg (range: 21 000 mg to 42 000 mg/70 kg) THC, based on a conversion factor between three and six fold for intravenous to inhaled routes of administration, and between 10 and 20 fold for intravenous to oral routes [583, 1658].

Significant CNS symptoms are observed with oral doses of 0.4 mg/kg (28 mg/70 kg) dronabinol (Marinol®). Signs and symptoms of severe intoxication with Marinol® include decreased motor coordination, lethargy, slurred speech and postural hypotension [227].

CBD

LD_{50} values after single IV doses of CBD were 50 mg/kg (285 mg/70 kg)[ii] in mice [1659], 232 to 252 mg/kg (2 619 to 2 845 mg/70 kg)[ii] in rats [431], and 212 mg/kg (4 787 mg/70 kg)[ii] in monkeys [1660]. There were no deaths in rats and monkeys given daily oral doses of 25 to 300 mg/kg of CBD (282 mg to 6 774 mg/70 kg)[ii] for 90 days [431]. In human studies, CBD given once at oral doses of 15 to 160 mg, inhaled at a dose of 0.15 mg/kg (10.5 mg/70 kg)[ii], or injected IV at doses of 5 to 30 mg did not produce adverse effects. In a case report, a teenager suffering from schizophrenia who received up to 1 500 mg/day of CBD had no adverse events [1490]. In one study by Devinsky et al. [262], the mean CBD dose at 12 weeks was 22.9 mg/kg (1 603 mg/70 kg)[ii] in patients with treatment-resistant epilepsy with 48 patients receiving up to 50 mg/kg/day (3 500 mg/70 kg)[ii] CBD escalated over a 12-week period. Adverse events were reported in 79% of patients, but most of them were mild or moderate and transient. Serious adverse events possibly related to CBD use were recorded in 20 patients (12%) and included status epilepticus, diarrhea, pneumonia, and weight loss. A post-hoc analysis showed that the CBD dose at week 12 was not correlated with the number of reported adverse events overall [262].

[ii] Human equivalent doses were calculated based on body surface area: animal doses in mg/kg were divided by 12.3 for mice, 6.2 for rats, and 3.1 for monkeys [1661]

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