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

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

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

4.8.6 Alzheimer's disease and dementia

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

The endocannabinoid system and Alzheimer's disease

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

Pre-clinical data

Pre-clinical studies suggest the endocannabinoid system protects against excitotoxicity, oxidative stress, and inflammation—all key pathological events associated with the development of AD (704). However, limited information exists regarding the use of cannabis or cannabinoids in the treatment of AD. Results from *in silico* and *in vitro* experiments suggest Δ^9-THC could bind and competitively inhibit acetylcholinesterase (AChE), which in the context of AD functions as a molecular chaperone accelerating the formation of amyloid fibrils and forming stable complexes with Aβ (705). Δ^9-THC blocked the amyloidogenic effect of AChE, thereby diminishing Aβ aggregation (705). Other *in vitro* studies suggest that cannabidiol may have neuroprotective, anti-oxidant, and anti-apoptotic effects, as well as preventing tau protein hyperphosphorylation in cellular models of AD (706,707,708). Endocannabinoids have also been shown to prevent Aβ-induced lysosomal permeabilization and subsequent neuronal apoptosis *in vitro* (704). In pre-clinical animal models of AD, cannabidiol dose-dependently and significantly inhibited reactive gliosis and subsequent neuroinflammatory responses in Aβ-injected mice, at doses of 2.5 mg/kg/day and 10 mg/kg/day i.p., during a seven-day course of treatment (709). Another study using both *in vitro* and *in vivo* models of AD reported opposing roles for the CB_1 and CB_2 receptors in this context: CB_1 receptor agonism and CB_2 receptor antagonism were both associated with blunted Aβ-induced reactive astrogliosis and attenuation of neuroinflammatory marker expression (710).

Clinical data

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

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

4.8.7 Inflammation

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

4.8.7.1 Inflammatory skin diseases (dermatitis, psoriasis, pruritus)

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

Pre-clinical and clinical studies

The results from pre-clinical studies on the role of cannabinoids in the modulation of cutaneous allergic reactions are mixed. Some studies suggest a protective role for certain cannabinoids, while others suggest an antagonistic role (reviewed in (41)). In clinical studies, experimentally-induced histamine-triggered pruritus was reduced by peripheral administration of the potent synthetic CB_1/CB_2 cannabinoid receptor agonist HU-

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

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

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

The endocannabinoid system and gastrointestinal disorders

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

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

4.8.8.1 Irritable bowel syndrome

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

Pre-clinical data

A few pre-clinical studies in animal models of IBS have been carried out to date. Two studies have employed mechanically-induced colorectal distension to trigger an acute visceral pain response in rodents as a model of IBS-associated visceral hypersensitivity. One study in rats showed that intra-peritoneal injection of different synthetic cannabinoid receptor agonists inhibited pain-related responses to experimentally-induced colorectal distension when administered *prior* to the experimental stimulus (734). Intravenous administration of different synthetic cannabinoid receptor agonists also appeared to inhibit the overall pain-related responses to experimentally-induced colorectal distension in rats, as well as in mice, when administered *after* the experimental stimulus (735). In another study, subcutaneous administration of CB_1 or CB_2-selective agonists was reported to reduce the enhanced small intestinal transit observed in a mouse model of post-inflammatory IBS (736).

Clinical data with dronabinol

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

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

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

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

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

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

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

The endocannabinoid system and IBD

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

Pre-clinical data

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

Acute colitis

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

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

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

Acute colitis and cannabidiol

Intra-peritoneal injection of cannabidiol (5 - 10 mg/kg) prior to DNBSA-induced acute colitis was associated with a significant attenuation of body weight loss caused by DNBSA (757). Cannabidiol (CBD) also reduced the wet weight/colon length ratio of inflamed colonic tissue, a marker of the severity and extent of the inflammatory response (757). Furthermore, CBD (5 - 10 mg/kg) significantly reduced macroscopic damage associated with DNBSA administration (mild edema, hyperemia, and small bowel adhesions) as well as microscopic damage (epithelium erosion, and mucosal and sub-mucosal infiltration of inflammatory cells with edema) (757). Lastly, treatment with CBD significantly attenuated the observed increases in some biological markers associated with inflammation and oxidative stress, as well as attenuating the observed increases in the colonic levels of anandamide and 2-AG (757).

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

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

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

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

Chronic colitis

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

Ileitis

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

Clinical studies with THC

A double-blind, randomized, placebo-controlled, crossover 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 (762). However, the authors did note a bias in the patient selection criteria which could have explained the apparent lack of effect.

Surveys and clinical studies with cannabis

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 (157). In contrast to patients with Crohn's disease, a greater proportion of patients with ulcerative colitis reported using cannabis to improve diarrheal symptoms (157). 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 inflammatory bowel disease questionnaire) score (157). Both ulcerative colitis and Crohn's disease patients reported using cannabis to improve stress levels and sleep (157). 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 (157). The vast majority (77%) of users reported smoking the cannabis as a joint without tobacco, 18% of users smoked it with tobacco, 3% used a water pipe, and 1% reported oral ingestion (157). 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 (157).

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 (248). 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 (248). Most patients smoked cannabis as joints (0.5 g cannabis/joint), a few inhaled the smoke through water, and one patient consumed cannabis orally (248). 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: 2 months - 9 years). All patients reported that consuming cannabis had a positive effect on their disease activity (248). 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 (248). The study was limited by design and small size.

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

Note: for sections 4.8.8.3, 4.8.8.4, and 4.8.8.5 below, no clinical studies examining the role of cannabis in the treatment of these disorders have been carried out to date.

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

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 (763)). CB_2 receptors are undetectable in normal liver but, like the CB_1 receptors, they are upregulated in pathological conditions; these include non-alcoholic fatty liver disease (NAFLD), liver fibrosis, regenerating liver, and hepatocellular carcinoma (reviewed in (763)). Increases in the concentrations of the endocannabinoids anandamide and 2-AG in the liver appear to vary depending on the pathophysiological condition in question (33).

Steatosis and fibrosis

Mounting evidence suggests an important role for the endocannabinoid system in the pathophysiology of a multitude of diseases affecting the liver (33). In general, the 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, 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 (33) and see also (249,250,251,764)). 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 (249,765).

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 (766). CBD dose-dependently triggered the apoptosis of cultured, activated hepatic stellate cells isolated from the livers of rats chronically exposed to an ethanol diet (766). The activation of hepatic stellate cells in response to liver injury is considered a key cellular event underlying hepatic fibrogenesis (766). 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 (766).

Ischemia-reperfusion injury and hepatic encephalopathy

Pre-clinical studies also indicate a protective role for CBD in hepatic ischemia/reperfusion injury, and hepatic encephalopathy, in mice and rats (767,768,769). 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 (767). 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 (767). 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 (767). 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 (768). 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 (768). Administration of Δ^8-tetrahydrocannabivarin (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 (770). Administration of Δ^8-tetrahydrocannabivarin *post-ischemia* attenuated, although to a lesser degree, the hepatic injury measured at 6 h of reperfusion (770). Pre-treatment with Δ^8-tetrahydrocannabivarin 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 (770).

Intra-peritoneal administration of CBD (5 mg/kg, i.p.) improved neurological, locomotor, and cognitive functions in a mouse model of fulminant hepatic encephalopathy (769). CBD also attenuated the degree of astrogliosis, but did not affect the extent and severity of necrotic lesions in the liver (769). CBD partially restored whole brain 5-HT levels, as well as the levels of markers of liver function (ammonia, bilirubin, AST, ALT) in affected mice (769).

4.8.8.4 Metabolic syndrome, obesity, diabetes

The endocannabinoid system and energy metabolism

Increasing evidence suggests an important role for the endocannabinoid system in the regulation of energy balance; dysregulation of the system is associated with the development of metabolic syndrome and obesity, and may also increase the risk of developing atherosclerosis and type-2 diabetes (11,17,771). 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 (772).

The regulation of energy balance by the endocannabinoid system 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 (11,17,771,773). In general, overactivity of the endocannabinoid system is associated with increased nutrient intake, enhanced energy storage, and reduced energy expenditure (17). Endocannabinoid tone appears to be modulated by hormones and peptides including leptin, insulin, ghrelin, and corticosteroids (17). 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 (774).

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 (23). 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 (11,775,776,777). In rats, central stimulation of the CB_1 receptor was associated with the development of hepatic and adipose tissue insulin resistance (772). 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 (391,775,778). 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 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 (779). Similarly, partial targeted deletion of the CB_1 receptor gene 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 (777).

Targeted deletion of the CB_1 receptor gene in mouse liver is associated with the development of diet-induced obesity, but retention of glucose, insulin and leptin sensitivity and lipid indices; targeted hepatic re-expression of the CB_1 receptor gene in CB_1 receptor gene knockout mice was associated with glucose intolerance and insulin resistance in response to a high-fat diet, but maintenance of proper body weight (780,781). Studies with CB_1 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 diet-induced obesity (391,782,783,784,785,786,787,788). Clinical studies with the CB_1 antagonist rimonabant have strongly supported the data gathered from animal studies (789,790,791,792,793,794,795).

Taken together, the above findings suggest an important role for the CB_1 receptor, both centrally and peripherally, in regulating energy balance; stimulation of the CB_1 receptor promotes energy storage and lipogenesis, whereas CB_1 receptor antagonism has the opposite effects. Consistent with these findings, 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 4.3.1 and 4.3.2, respectively). Yet curiously, despite these beneficial effects on body weight in clinical disorders, a number of studies have so far failed to find an association between overweight/obesity and consumption of cannabis in the general population (796,797). In fact, the prevalence of obesity appeared 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 (797).

Role of the CB_2 receptor

The CB_2 receptor also appears to also play an important role in energy balance (798). 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 (798). 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 (798). Conversely, administration of a CB_2-selective antagonist reduced inflammation both in adipose tissue and liver of obese animals (798). 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 (798). CB_2 knockout mice on a high-fat diet also exhibited minimal hepatic steatosis compared to wild-type mice (798). Mice deficient in CB_2 receptor expression also exhibited increased food intake and body weight with age compared to wild-type mice (799). The CB_2 receptor knockout mice did not develop insulin resistance and showed enhanced insulin-stimulated glucose uptake in skeletal muscle (799). Taken together, these results suggest an important and complex role for the CB_2 receptor in energy balance and obesity, although further studies are needed to better understand its role.

Other cannabinoids

Pure Δ^9-tetrahydrocannabivarin (THCV) administered i.p. (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 when a botanical extract containing both Δ^9-THCV and Δ^9-THC was used (92). Inclusion of cannabidiol 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 (92). 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 (800).

4.8.8.5 Diseases of the pancreas (diabetes, pancreatitis)

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 endocannabinoid system 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 endocannabinoid system (774,801,802).

Function of the endocannabinoid system in the pancreas

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 (801,803) (and also reviewed in (774)). More recently, the endocannabinoid 2-arachidonoylglycerol (2-AG) has been implicated in the regulation of both insulin and glucagon secretion in human pancreas (802).

Intra-muscular administration of cannabis resin (containing 6.3% Δ^9-THC, 3.2% cannabidiol, and 1.9% cannabinol) 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 (804). 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 (805). In humans, intravenous injection of 6 mg of Δ^9-THC to healthy, non-obese male volunteers was associated with acute impairment of glucose tolerance in response to glucose challenge with no change in plasma insulin levels (806).

Survey data

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

Cannabis, the endocannabinoid system, and acute and chronic pancreatitis

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

Pre-clinical data and acute or chronic pancreatitis

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

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

4.8.9 Anti-neoplastic properties

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

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

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

Pre-clinical data

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

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

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

Combining cannabinoids with other chemotherapeutic agents

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

Clinical data

There is only one report of a clinical study of Δ^9-THC to treat cancer (836). In this non-placebo controlled pilot study, nine patients with glioblastoma multiforme who had failed standard surgical and radiation therapy, had clear evidence of tumour progression, and had a minimum Karnofsky score of 60 were treated with 20 - 40 μg Δ^9-THC intra-tumourally per day (with doses of up to 80 - 180 μg Δ^9-THC per day). Median treatment duration was 15 days (836). While intra-tumoural administration of Δ^9-THC appeared to be well tolerated, the effect of Δ^9-THC on patient survival was not significantly different from that observed in other studies using chemotherapeutic agents such as temozolomide or carmustine (837,838). Nevertheless, *in vitro*, Δ^9-THC inhibited the proliferation and decreased the viability of tumour cells isolated from glioblastoma biopsies, most likely through a combination of cell-cycle arrest and apoptosis (836,839). In addition, results from a separate *in vitro* study suggest that CBD enhanced the inhibitory effects of Δ^9-THC on human glioblastoma cell proliferation and survival (839).

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

4.8.10 Emerging Potential Therapeutic Uses

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

5.0 Precautions

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

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

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

6.0 Warnings

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

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

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

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

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

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

6.1 Tolerance, dependence, and withdrawal symptoms

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

6.2 Drug interactions

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

Xenobiotic-mediated inhibition or potentiation of cannabinoid metabolism

Δ^9-THC is oxidized by the xenobiotic-metabolizing cytochrome P450 (CYP) mixed-function oxidases 2C9, 2C19, and 3A4 (62). Therefore substances that inhibit these CYP isoenzymes such as certain anti-depressants (e.g. fluoxetine, fluvoxamine, and nefazodone), proton pump inhibitors (e.g. cimetidine and omeprazole), macrolides (e.g. clarithromycin and erythromycin), anti-mycotics (e.g. itraconazole, fluconazole, ketoconazole, miconazole), calcium antagonists (e.g. diltiazem, verapamil), HIV protease inhibitors (e.g. ritonavir), amiodarone, and isoniazid can potentially increase the bioavailability of Δ^9-THC as well as the chance of experiencing THC-related side effects (289,875,876). On the other hand, drugs that accelerate Δ^9-THC metabolism via 2C9 and 3A4 isozymes such as rifampicin, carbamazepine, phenobarbital, phenytoin, primidone, rifabutin, troglitazone, and Saint John's Wort may conversely decrease the bioavailability of THC and hence its effectiveness if used in a therapeutic context (289,876).

Cannabinoid–mediated regulation of drug metabolism and drug transport

THC, CBD, and CBN are known to inhibit CYP isozymes such as CYP1A1, 1A2, and 1B1 (58). Cannabis may therefore increase the bioavailability of drugs metabolized by these enzymes. Such drugs include amitryptiline, phenacetin, theophylline, granisetron, dacarbazine, and flutamide (58). THC, carboxy- Δ^9-THC, CBD, and CBN all stimulate, and in some cases even inhibit, the activity of the drug transporter P-glycoprotein *in vitro* (56). This suggests a potential additional role for these cannabinoids in affecting the therapeutic drug efficacy and toxicity of coadministered drugs (56). Clinicians should therefore be aware other medications that the patient is taking and carefully monitor patients using other drugs along with cannabis or cannabinoids.

Cannabinoid-opioid interaction

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

Evidence from pharmacogenetic studies

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

Data from clinical studies

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

6.3 Drug screening tests

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

7.0 Adverse Effects

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

7.1 Carcinogenesis and mutagenesis

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

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

7.2 Respiratory tract

Differences in the smoking techniques used by cannabis vs. tobacco smokers are reported to result in three-fold higher levels of tar, and five-fold higher levels of carbon monoxide being retained in the lungs during cannabis smoking compared to tobacco smoking (885). A systematic comparison of the mainstream smoke composition from cannabis (Health Canada product) and tobacco cigarettes (prepared in the same way and consumed in an identical manner), under two different sets of smoking conditions ("standard" and "extreme") has been reported (70). The "standard" condition reflects typical tobacco cigarette smoking conditions, whereas the "extreme" condition approaches that typically seen in cannabis smoking (70). Ammonia in mainstream cannabis smoke was 20-fold greater than that found in tobacco smoke, and oxides of nitrogen and hydrogen cyanide were three to five times higher in cannabis smoke vs. tobacco smoke. Carbon monoxide was significantly lower in mainstream cannabis smoke, under both smoking conditions. Tar was statistically significantly higher in mainstream cannabis smoke but only under the "extreme" smoking condition.

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

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

7.3 Immune system

Pre-clinical studies

Evidence from *in vivo* and *in vitro* studies suggests complex and apparently dichotomous roles for the endocannabinoid system on immune system function (24). First, CB_1 and CB_2 receptors are known to be expressed in various immunocytes (B cells, monocytes, neutrophils, T lymphocytes, macrophages, mast cells), with CB_2 receptor expression generally being more abundant than CB_1 receptor expression; the ratio of CB_2 to CB_1 receptor expression ranges between 10 - 100 : 1 respectively, depending on the immune cell type in question (24,25). Second, immune cells also have the ability to synthesize, secrete, transport and catabolize endocannabinoids (24). Third, while stimulation of the CB_2 receptor appears to be generally associated with immunosuppressive effects, activation of the CB_1 receptor appears to be associated with an opposing immunostimulatory effect (24). Fourth, whereas certain cannabinoids have been shown to modulate the release of pro- or anti-inflammatory cytokines, pro-inflammatory cytokines (such as TNF-α) have, in turn, been reported to affect the functioning of the endocannabinoid system by upregulating the expression of both CB_1 and CB_2 receptor mRNA and protein levels (25). Thus, there appears to be some level of cross-talk between the endocannabinoid and immune systems. Fifth, as is the case in other situations, Δ^9-THC appears to have a biphasic effect on immune system function. Low doses of Δ^9-THC seem to have stimulatory or pro-inflammatory effects, while higher doses appear to have inhibitory or immunosuppressive effects (266). Both Δ^9-THC and CBD have been reported to modulate cell-mediated and humoural immunity, through CB receptor-dependent and CB receptor-independent mechanisms (266,892,893). Cannabinoids target various cellular signaling and transcriptional pathways resulting in the inhibition of pro-inflammatory cytokine release (e.g. IL-1β, IL-6, IFN-β), and/or stimulation of anti-inflammatory cytokine release (e.g. IL-4, IL-5, Il-10, IL-13) (25,266). CBD also appears to induce a shift in Th1/Th2 immunobalance (892). While under certain circumstances, cannabinoids may appear to have broad anti-inflammatory and immunosuppressive functions which could be of benefit in pathological conditions having inflammatory characteristics, such beneficial functions may become problematic in the context of essential defensive responses to infections (24). For example, *in vitro* as well as *in vivo* experiments suggest cannabinoids have an impact on virus-host cell interactions (894): cannabinoid treatment was associated with increased viral replication of HSV-2, HIV-1, KSHV, influenza, and VSV viruses, or was associated with increases in surrogate measures of infection in these experimental models (895,896,897,898,899,900).

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

Clinical studies

The effects of cannabis smoking on the human immune system have been studied, but to a very limited degree. A major concern with HIV-positive cannabis smokers, or patients undergoing cancer chemotherapy, is that they might be more vulnerable than other cannabis smokers to the immunosuppressive effects of cannabis or that they risk exposure to infectious organisms associated with cannabis plant material (378). A group of studies has partially addressed the former concern. In one study, HIV-positive patients on stable anti-retroviral therapy were randomized to smoked cannabis or oral dronabinol and showed no changes in CD4+ and CD8+ T-cell, B cell, or NK cell counts and a number of other parameters compared with placebo, over a 21-day study period (901). A longitudinal study of 481 HIV-infected men who used cannabis and who were followed over an average five-year period found that while cannabis use was generally associated with a higher CD4+ cell count in infected men and controls, no clinically meaningful associations, adverse or otherwise, between cannabis use and T-cell counts and percentages could be established (902). Cannabis use was also not associated with an increased rate of progression to AIDS in HIV-infected individuals (903). In another study, smoking cannabis was associated with lower plasma concentrations of the protease inhibitors indinavir and nelfinavir; dronabinol or placebo had no effect (322). However, the decreased protease inhibitor levels were not associated with an elevated viral load, or changes in CD4+ or CD8+ cell counts (390).

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

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

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

7.4 Reproductive and endocrine systems

Role of the endocannabinoid system in sexual physiology

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

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

Effects of cannabis on human sexual behaviour

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

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

Effects on sperm and testicular health

The effects of cannabis and Δ^9-THC on human sperm have been investigated both *in vivo* and *in vitro* (907,908,909). A significant decline in sperm count, concentration and motility, and an increase in abnormal sperm morphology were observed in men who smoked cannabis (8 - 20 cigarettes/day) for four weeks (907). In an *in vitro* study, sperm motility and acrosome reactions were decreased in both the 90% and 45% sperm fractions, the 90% fraction being the one with the best fertilizing potential and the 45% fraction being a poorer sub-population (909). Decreased sperm motility was observed in both fractions at Δ^9-THC concentrations mimicking those attained recreationally (0.32 and 4.8 μM), and in the 45% fraction at Δ^9-THC concentrations typically seen therapeutically (0.032 μM). Inhibition of the acrosome reaction was only observed at the highest Δ^9-THC concentration tested (4.8 µM) in the 90% fraction, while the 45% fraction displayed decreased acrosome reactions at all three Δ^9-THC concentrations tested. Such effects carry the possibility of impairing crucial sperm functions and male fertility, especially in those males already on the borderline of infertility (909).

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

Effects on foetal development and child development

Results from human epidemiological studies examining short-term neonatal outcomes among women who smoked cannabis during pregnancy are equivocal; some report reduced neonatal birth weight and length (911,912,913,914) or a slightly increased risk of sudden infant death (915), while others report no effect (916,917,918). On the other hand, there appear to be some long-term effects on the development of children born to mothers who used cannabis during pregnancy. Two longitudinal investigations carried out over a time span of 20 years (reviewed in (869)) suggest that such *in utero* exposure impacts negatively on attentional behaviour and visual analysis and hypothesis testing, but not on standardized derived IQ scores. These findings were confirmed by a third study (870). These behavioural effects also appeared to have an adverse influence on aspects of executive function in later years.

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

7.5 Cardiovascular system

The most consistent acute physiological effect of smoking cannabis is dose-related tachycardia (121,226,232). While this is not usually considered dangerous for healthy young users, it may be dangerous to those already suffering from cardiac disorders or angina (118,921). Inhalation of cannabis smoke reduces the amount of exercise required to cause an angina attack by 50% (922), and has been associated with a five-fold increased risk of myocardial infarction in the first hour following smoking (232). This may be caused by a Δ^9-THC-related increase in cardiac output, myocardial oxygen demand, catecholamine levels, and carboxyhemoglobin as well as postural hypotension (226,227,923). While tachycardia is observed in both occasional and chronic users, tolerance develops relatively quickly with the degree of tachycardia diminishing with use. After about 8 to 10 days of constant dosing with 10 mg of Δ^9-THC per day (equivalent to 80 - 100 mg of cannabis containing 10% Δ^9-THC), bradycardia (924) with a decrease in supine blood pressure was observed (925).

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

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

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

7.6 Gastrointestinal system and Liver

7.6.1 Hyperemesis

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

7.6.2 Liver

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

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

7.7 Central nervous system

The most frequently reported adverse events encountered with cannabinoids involve the central nervous system (CNS). Commonly reported CNS events in controlled clinical trials with dronabinol (Marinol®) and nabiximols (Sativex®) are intoxication-like reactions including drowsiness, dizziness, and transient impairment of sensory and perceptual functions (174,290). A "high" (easy laughing, elation, heightened awareness), which could be unwanted or unpleasant for patients, was reported in 24% of the patients receiving Marinol® as an anti-emetic, and in 8% of patients receiving it as an appetite stimulant (174). Other adverse events occurring at a rate of > 1% for Marinol® include anxiety/nervousness, confusion, and depersonalization (174). Dizziness, euphoria, paranoia, somnolence, abnormal thinking ranged from 3 - 10% (174). The rates of amnesia, ataxia, and hallucinations were > 10% when used as an anti-emetic at higher doses (174). Dizziness is the most common intoxication effect with Sativex®, reported initially in 35% of patients titrating their dose; the reported incidence of this effect in long-term use is approximately 25% (940). All other intoxication-like effects are reported by less than 5% of users (with the exception of somnolence, 7%) (940). Other events reported for Sativex® include disorientation and dissociation. **Many, if not all, of the above-noted CNS effects also occur with cannabis.**

7.7.1 Cognition

The acute effects of cannabis use on cognition have been reviewed by Lundqvist (235). Cannabis impairs cognition involving faculties such as short-term memory, attention, concentration, executive functioning and visuoperception (180,941,942). The digit span task has been used to estimate the effects of cannabis on recent memory, but results have been inconsistent. Differences may be due to the dosage used, the smoking procedure, or whether the digit span task assesses forward or backward recall (943). Cannabis intoxication significantly impairs the ability to learn and recall word lists or short stories (944).

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

7.7.2 Psychomotor performance

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

A double-blind, placebo-controlled, crossover study comparing the effects of a medium dose of dronabinol (20 mg) and of two hemp milk decoctions, containing medium (16.5 mg) or high doses (45.7 mg) of THC, reported severe impairment on several performance skills required for safe driving (953). A "moderate" dose (21 mg of THC) was associated with impairments in motor and perceptual skills necessary for safe driving (954). In one study, performance impairment appeared to be less significant among heavy cannabis users compared to occasional users, potentially because of the development of tolerance or compensatory behaviour (169). It has been suggested that, unlike alcohol, cannabis users are aware of their level of intoxication and compensate by becoming hyper-cautious; in tasks such as driving, this kind of behaviour results in decreased speed, decreased frequency of overtaking, and an increase in following distance (955,956). Others disagree with this assertion ((957) and also see (176)).

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

A recent case-control study estimating accident risk for a variety of substances including alcohol, medicines, and illegal drugs found that the odds ratio for accident risk for all the THC concentrations measured (1 to > 5 ng/mL) was statistically significant (959). At whole-blood concentrations of ≥ 2 ng/mL THC, the risk of having an accident was significantly increased (959). One study found that the risk of responsibility for fatal traffic crashes, while driving under the influence of cannabis, increased with increasing blood concentrations of THC such that there was a significant dose-effect relationship between risk of responsibility for fatal traffic crashes and blood concentrations of THC. The study showed that the odds ratio of having a fatal crash increased from 2.18 if blood concentrations ranged between 0 and 1 ng/mL of THC, to 4.72 if blood THC concentrations were ≥ 5 ng/mL (960). The findings from this study further support the notion of a causal relationship between cannabis use and crashes (960). Another study suggested that drivers who were judged (by a police physician) as being impaired had higher blood THC concentrations than drivers judged not to be impaired (median: 2.5 ng/mL vs. 1.9 ng/mL) (961). Using a binary logistic regression model, the odds ratio for being judged impaired appeared to increase with increasing drug concentrations from 2.9 ng/mL onwards (961). Serum THC concentrations between 2 and 5 ng/mL have been identified as a threshold above which THC-induced impairment of skills related to driving become apparent (133,959). Performance impairment after cannabis intake was reported to be highest during the first hour after smoking, and between 1 - 2 h after oral intake, and declining after 3 - 4 h (or longer in the case of oral ingestion) (862,961).

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

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

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

7.7.3 Psychiatric effects

7.7.3.1 Acute psychotic reactions

Cannabis and cannabinoid use has been linked to episodes of acute psychosis in both regular and drug-naïve users (122,145,962). In one report, two healthy patients who had participated in a randomized controlled trial (RCT) measuring the effects of orally administered cannabinoids (including dronabinol or cannabis decoctions) on psychomotor performance displayed acute psychotic reactions following exposure to cannabis (145). The subjects had no psychiatric history or concomitant drug use, but were "occasional" regular cannabis users. In another RCT, 22 healthy subjects, also with a history of occasional cannabis use, no concomitant drug use, and with no psychiatric disorders received intravenous doses of Δ^9-THC paralleling peak plasma THC levels achieved by smoking cannabis cigarettes containing 1 - 3.5% Δ^9-THC (140). Drug administration was associated with a range of acute, transient, behavioural, and cognitive effects including suspiciousness, paranoid and grandiose delusions, conceptual disorganization, and illusions. Depersonalization, derealization, distorted sensory perceptions, altered bodily perceptions, feelings of unreality, and extreme slowing of time were also reported. Furthermore, blunted affect, reduced rapport, lack of spontaneity, psychomotor retardation, and emotional withdrawal were observed. Another study reported similar results (963).

7.7.3.2 Anxiety, Depression and Bipolar Disorder

Anxiety and depression

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

Research on the topic of cannabis and depression is relatively scarce and conflicting. A 2003 review reported that the co-morbidity level between heavy or problematic cannabis use and depression, in surveys of the general population, exceeds what would be expected by chance (968). The authors also identify a modest association between early-onset regular or problematic use and later depression. However, limitations in the available research on cannabis and depression, including limitations in study design, as well as limitations in the ability to measure cannabis use, and limitations in the ability to measure depression were also highlighted. A U.S. study of adults using longitudinal national survey data (n = 8 759) found that the odds of developing depression in past-year cannabis users was 1.4 times higher than the odds of non-users developing depression (969). However, after adjusting for group differences, the association was no longer significant. In a 2008 study, the same group looked at the relationship between cannabis use and depression among youth using a longitudinal cohort of 1 494 adolescents. Similar to the adult study, the results did not support the causal relationship between adolescent-onset cannabis use problems and early adult depression (970). In contrast, another U.S. study based on the results of the National Epidemiological Survey on Alcohol and Related Conditions (n = 43 093) found that major depression was significantly associated with lifetime cannabis disorders and dependence (971). A 2007 study using data from the Netherlands Mental Health Survey and Incidence Study found a modest increased risk of a first depressive episode (Odds Ratio = 1.62; 1.06 - 2.48), after controlling for strong confounding factors (972). Of greater significance in this study was the strong increased risk of bipolar disorder (Odds Ratio = 4.98; 1.80 - 13.81) with cannabis use (see below for further information on cannabis and bipolar disorder). There was a dose-response relationship associated with the risk of 'any mood disorder' for almost daily and weekly users, but not for less frequent users. A survey of 248 French high school students found that cannabis users had significantly higher rates of suicidal behaviours and depressive and anxious symptoms compared to non-users (973). Another study suggested a putative positive association between exposure to cannabis and protracted suicidal thoughts or attempts in young people, although the study suffered from a number of limitations (974).

Bipolar disorder

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

One three-year, prospective study involving 4 815 subjects attempted to determine if baseline cannabis use increased the risk for development of manic symptoms, if the association between cannabis use and mania was independent of the emergence of psychotic symptoms, and if baseline mania predicted cannabis use at follow-up (975). The authors found that cannabis use at baseline was associated with follow-up mania (Odds Ratio = 5.32, 95% Confidence Interval: 3.59, 7.89). After adjusting for confounding factors, the association persisted although it was reduced (Odds Ratio = 2.70, 95% Confidence Interval: 1.54, 4.75). The risk of developing manic symptoms appeared to increase with increased baseline frequency of cannabis use (975). The effect size was largest for those who used cannabis 3 - 4 days/week, followed by those who used daily and 1 - 2 days/week, and lastly for those who used 1 - 3 days/month (975). The authors reported that manic symptoms at baseline did not predict cannabis use during follow-up. The results suggested that use of cannabis increased the risk of developing subsequent manic symptoms and that this effect was dose-dependent (975).

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

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

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

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

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

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

One study reported that when compared with controls, patients with bipolar disorder were almost seven times (95% Confidence Interval: 5.41 - 8.52) more likely to report a lifetime history of cannabis use (977). Furthermore, this association appeared to be gender-independent. Those patients who used cannabis after, or in tandem with, their onset of bipolar symptoms had a lower age at onset of the disorder (17.5 vs. 21.5 yrs) (977). Furthermore, those who used cannabis prior to the onset of a bipolar disease episode were 1.75 times (95% Confidence Interval: 1.05 - 2.91) more likely to report disability attributable to bipolar disorder (977).

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

7.7.3.3 Schizophrenia and psychosis

The endocannabinoid system has been implicated in the pathogenesis of schizophrenia and psychosis (please see section 4.8.5.5 for more information). Individuals with schizophrenia, or with a family history of this disorder, are likely to be at greater risk of suffering adverse psychiatric effects as a result of using cannabis or psychoactive cannabinoids such as Δ^9-THC (152). Heavy cannabis use can aggravate psychotic symptoms and cause more relapses, and those individuals who use cannabis are at an increased risk of a poor prognosis (118,138,984,985). Self-reported use of cannabis in adolescence has been associated with an increased risk of developing schizophrenia, and this risk was related to frequency of cannabis exposure (986). A cohort study of over 1 000 children followed from birth to age 26 reported a three-fold increased risk of psychotic disorders in those who used cannabis, and suggested that cannabis exposure among psychologically vulnerable adolescents should be strongly discouraged (987). The relationship between cannabis use and psychotic symptoms was also studied in a cohort of 2 437 young people (ages 14 - 24 yrs) who had greater than average pre-disposition for psychosis, and who had first used cannabis during adolescence (146). The authors found a dose-response relationship between frequency of cannabis use and the risk of psychosis. The effect of cannabis use was also much stronger in those individuals with a pre-disposition for psychosis. A systematic review of evidence pertaining to cannabis use and the occurrence of psychotic or affective mental health outcomes reported an increased risk of any psychotic outcome in individuals who had ever used cannabis compared with non-users (Odds Ratio = 1.41) (141). Furthermore, the findings appeared to show a dose-related effect, with greater risk to individuals who used cannabis most frequently (Odds Ratio = 2.09) (149,150).

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

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

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

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

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

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

Schizophrenia and the Brain-Derived Neurotrophic Factor gene

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

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

7.7.3.4 Amotivational syndrome

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

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

8.0 Overdose/Toxicity

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

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