

Supplementary Figures and Tables

Table #1:

<i>Province</i>	<i>Medical Marijuana Policies</i>
<i>Alberta</i>	Physicians must register with the College of Physicians and Surgeons of Alberta prior to authorizing medical Marijuana
<i>British Columbia</i>	Physicians must do an addiction risk assessment using a validated addiction risk tool prior to authorizing medical marijuana. Physicians must access the province's drug registry (PharmaNet) to document that conventional therapies have failed.
<i>Prince Edward Island</i>	Authorizations for medical cannabis cannot be provided to patients via telehealth. Patients must consent to their names being given to the College of Physicians and Surgeons of Prince Edward Island.
<i>Québec</i>	Access to medical marijuana may only be provided as part of a recognized research project and only for specific conditions.

Table #2:

Adverse Effects On:	Health Canada Summary¹	New Study Results	Level of Evidence
Carcinogenesis and mutagenesis	Some studies have suggested an increased incidence of prostate, ² head and neck, ³ and lung cancer. ⁴ However, further well-controlled epidemiological studies are required. Health Canada recommends limiting the degree to which cannabis is smoked as evidence regarding its carcinogenic potential is inconsistent. Cannabis smoke cannot be considered safer than tobacco smoke. Some studies have shown cannabis smoke to contain many of the same chemicals as tobacco smoke. ⁵ Vaporization of cannabis may be a better option as this lower-temperature process produces smaller quantities of toxic by-products. ⁶⁻⁹		
Respiratory tract	Cannabis vs. tobacco smokers retain three-fold higher levels of tar, and five-fold higher levels of carbon monoxide due to differences in smoking topography. ¹⁰ Chronic cannabis only smokers show numerous histopathologic changes on mucosal biopsy (e.g. basal cell hyperplasia and squamous cell metaplasia). ¹¹ Mild changes in pulmonary function have been found in heavy cannabis smokers, ¹²⁻¹⁴ and risk of developing chronic obstructive pulmonary disease later in life may be as great as tobacco smokers. ¹⁵ Further research must be conducted to clarify the relationship between cannabis smoking and development of lung disease.	Hancox <i>et al.</i> ¹⁶ found that frequent cannabis smoking was associated with symptoms of morning cough, sputum production, and wheeze (all $p < 0.001$). However, these symptoms could either improve or worsen with cannabis smoking cessation or continued use, respectively.	1b
Immune system	Pre-clinical trials have shown cannabinoids to have both immunosuppressive and immunostimulatory effects depending on type, dose, route of administration, length of		

	<p>exposure, and receptors targeted.^{17,18} This immunosuppressive function could be beneficial in conditions having inflammatory characteristics, but problematic when a defense response is necessary as in the case of infection.¹⁷ Cannabinoids, in <i>in vitro</i> and <i>in vivo</i> experiments, have been suggested to impact virus-host interactions,¹⁹ resulting in increased viral replication of HSV-2, HIV-1, KSHV, influenza, and VSV.²⁰⁻²⁵ The limited number of human clinical trials pertaining to cannabis use in immunosuppressed individuals, specifically HIV-positive individuals, have shown that cannabis either had no effect on CD4+,²⁶ or increased CD4+ with no clinically meaningful associations.²⁷ Cannabis was not associated with increased rates of progression to AIDS,²⁸ but smoking cannabis did show association with lower plasma concentrations of protease inhibitors indinavir and nelfinavir+, as compared to dronabinol and placebo which had no effect.²⁹ This decrease in protease inhibitor levels were not associated with elevation in viral load or changes in CD4+ or CD8.³⁰ One study also showed that HIV-positive patients who were diagnosed with cannabis use disorder had significantly lower adherence to anti-retroviral therapy, had higher viral load, and reported significantly more frequent and severe HIV symptoms or medication side effects than those who used cannabis less than daily or not at all.³¹ Smoking cannabis was also associated with poorer outcomes in patients with chronic hepatitis C.^{32,33} Therefore, Health Canada recommends clinicians to weigh the potential benefits against the possible risks for each individual patient they consider placing on cannabis and/or cannabinoid therapy.</p>	
Reproductive and endocrine system	<p>Experiment evidence suggests that the endocannabinoid system is located in the male and female reproductive systems and regulates various functions such as folliculogenesis, spermatogenesis, ovulation, fertilization, oviductal transport, implantation, embryo development, pregnancy, and labour.³⁴ The CB₁ receptors are also found to be in the brain in regions which affect, regulate, or modulate aspects of sexual behavior and function, such as the hypothalamic-pituitary-gonadal axis (HPG axis), genital reflexes, and sexual motivation and inhibition.^{35,36} The modulation of the HPA axis can result in hormonal suppression of luteinizing hormone, thyroid stimulation hormone, growth hormone, and prolactin, with probable suppression of follicle stimulating hormone as well.^{37,38} Studies showing the effects of cannabis on human sexual behavior and functioning have concluded that it appears to be dose-dependent;³⁵ low to moderate doses having beneficial effects, such as reported increases in sensitivity to touch and relaxation corresponding to increase in sexual responsiveness, and higher doses having the opposite response, such as inhibiting sexual motivation and erectile function. Currently, studies looking at the effects of cannabis consumption on testosterone levels are inconsistent.³⁵ However, <i>in vivo</i> and <i>in vitro</i> studies have shown cannabis and Δ^9-THC to significantly decline sperm</p>	<p>Morrison <i>et al.</i>⁴³ explored the risk and protective factors associated with consistent contraceptive use. They looked at 18 to 24 year old females attending a 4-year college or university full time and reporting having vaginal intercourse with a male in the past 12 months. Almost 25 % of participants had used cannabis in the past 30 days with less than 4% using it daily. Frequency of cannabis use was found to relate to contraceptive use inversely, with more</p>

	count, concentration and motility, and increase the abnormal sperm morphology. ³⁹⁻⁴¹ A case-control study by Lacson <i>et al.</i> ⁴² has shown there to be nearly a two-fold increased risk of developing testicular germ-cell tumours of any histologic type and greater than two-fold increased risk of non-seminoma or mixed germ-cell tumors in men who had ever used cannabis compared to those who had never.	frequent cannabis use being associated with more inconsistent contraceptive use.	
Cardiovascular system	Inhalation of cannabis has been shown to cause dose-related tachycardia in both occasional and chronic users. ⁴⁴⁻⁴⁶ However, tolerance can develop with studies showing that after 8 to 10 days of constant dosing with 10 mg of Δ^9 -THC per day, bradycardia, ⁴⁷ and a decrease in supine blood pressure can be observed. ⁴⁸ Studies show that inhalation of cannabis smoke can have many effects, especially in those with heart disease. Such effects are: reduction in the amount of exercised needed to cause an angina attack by 50%, ⁴⁹ a five-fold increased risk of myocardial infarct within first hour of smoking, ⁴⁶ peripheral vasodilation, ⁵⁰ postural hypotension, ⁵⁰ conjunctival reddening, ⁵⁰ arteritis, ⁵¹⁻⁵⁴ multi-focal intracranial stenosis, ⁵⁵ and stroke. ^{56,57}	A systematic review performed by Jouanous <i>et al.</i> ⁵⁸ revealed that the use of cannabis-based products can have significant cardiovascular impact, most notably ischemic strokes. Ischemic strokes in young cannabis users were found to be most commonly due to intracranial arterial stenosis ($p < 0.00001$). The association between cannabis exposure and myocardial infarction was found to be weaker than related to strokes. Evidence and data of cannabis use on heart rhythm and cardiac function is limited.	1
Gastrointestinal system and liver	Studies have shown a significant association between daily cannabis smoking and moderate to severe fibrosis of the liver, ³² and it being a predictor of fibrosis progression, ³³ and steatosis severity; ⁵⁹ with strong recommendations for chronic hepatitis C patients to abstain from cannabis use. However, studies looking at moderate cannabis use (less than daily) have shown increased anti-retroviral treatment compliance duration attributed to the sustained absence of detectable levels of hepatitis C viral RNA six months after completion of therapy. ⁶⁰		
CNS: Cognition and psychomotor performance	The most commonly encountered adverse effects by patients using cannabinoids involve the central nervous system (CNS). Dronabinol and nabiximol controlled clinical trials have reported drowsiness, dizziness, and transient impairment of sensory and perceptual function. ^{61,62} Dronabinol has also shown to have adverse reactions such as a “high” (easy laughing, elation, heightened awareness), anxiety/nervousness, confusion, depersonalization, paranoia, somnolence, abnormal thinking, amnesia, ataxia, and hallucinations. ⁶¹ The most common adverse reaction	Dougherty <i>et al.</i> ⁸³ explored the cognitive and behavioral (attention, memory, decision-making, and impulsivity) effects of cannabis use in 14 to 17 year-olds. They found	3

experience by 35% of nabiximols users when initially titrating their dose is dizziness, which decreases to 25% of in the long-term.⁶³

Cannabis has been shown to impair short-term memory, attention, concentration executive functioning, and visuoperception.⁶⁴⁻⁶⁶ Its long-term effects on cognition are inconclusive with some studies showing no long-term cognitive decline, while others report cognitive deficits which can persist even after abstinence.^{64,66-68} One prospective longitudinal study looking at persistent cannabis use and neuropsychological functioning has reported that cannabis use beginning in adolescence was associated with significant global neuropsychological decline in many domains of functioning which were not fully restored after one or more years of cannabis cessation.⁶⁹

that these adolescent marijuana users exhibited impairment in sustained attention, decision-making, and intelligence, with short-term memory and impulse control being most significantly affected.

Psychomotor performance impairment has been shown to occur in individuals under the influence of cannabinoids.⁷⁰ There are no studies specifically looking at psychomotor performance in individuals using cannabis for solely medical purposes. However, a number of studies have been conducted related to the safety of driving under the influence of cannabis. Studies have reported dose-dependent impairment on several performance skills required for safe driving such as motor and perceptual skills,⁷¹⁻⁷⁶ with a dose-effect relationship between risk for car accident or fatal crash and blood concentrations of THC.⁷⁴⁻⁷⁹ Driving performance was further impaired with co-consumption of alcohol.⁸⁰ Other studies have shown that this performance impairment to be less significant among heavy cannabis users compared to occasional users, attributed to tolerance development or developed compensatory behaviours.^{81,82}

Table #3:

Reference	Indication	Medication	Outcome	Level of Evidence
84	Acute Pain	Smoked cannabis or Dronabinol	Drug effects in pain sensitivity and tolerance peaked 15 mins after MM was smoked and 180 mins after dronabinol was administered. High marijuana strength (3.56% THC) and dronabinol dose (20 mg) increased the latency to first reported pain 13.1 ±3.9 s and 12.1±5.6s, respectively (p ≤0.01). No difference in pain sensitivity between marijuana and dronabinol. Low marijuana dose and both dronabinol doses, 10 mg and 20 mg, increase pain tolerance versus placebo 4.9±3.4s, 2.8±2.9s and 6.1±4.4s from baseline, respectively (p≤0.05). Both marijuana strengths and high dose dronabinol decreased subjective pain intensity ratings (p≤0.001 and p≤0.05, respectively).	2
85	Neuropathic pain	Inhaled THC Δ ⁹ -	57% of low-dose (1.29% THC) and 61% high-dose (3.53% THC) experienced 30% pain	1

			reduction ($p<0.05$); however, no statistical significant difference between low- and high-doses ($p>0.7$)	
86	Neuropathic pain: peripheral	THC/CBD oromucosal spray	28% of treatment vs 16% of placebo group had 30% reduction in pain levels on the PNP 0-10 NRS; Intention-to-treat (ITT) analysis with odds ratio of 1.97 ($p=0.034$) Adjusted mean reduction in PNP 0-10 NRS (ITT analysis) -0.34 ($p=0.139$) in favour of benefit with treatment	1
87	Neuropathic pain: chemotherapy-induced	Sativex® oromucosal spray	Pain score (NRS-PI) decreased from 6.75 (baseline) \rightarrow 5.5 (mid-treatment) \rightarrow 6.00 (end of treatment) in the treatment group. Pain score decreased from 6.375 \rightarrow 6.31 \rightarrow 6.38 in placebo group ($p=0.007$). Five participants dropped ≥ 2 points on the NRS-PI scale. NNT = 5.	1
88	Neuropathic pain: diabetic Neuropathy	Aerosolized, inhaled Δ^9 -THC	Statistically significant decreases in spontaneous pain scores in placebo vs low-, medium-, and high-dose THC as well as high-dose versus low- and medium-dose THC ($p<0.05$) Statistically significant effect of high dose on foam brush and von Frey doses ($p<0.001$). Average pain intensity score for placebo was 0.44 ($p=0.031$), 0.42 ($p=0.04$), and 1.2 ($p<0.001$) points higher for low-, medium-, and high-doses.	1
89	Neuropathic pain: MS	Oral Δ^9 -THC tablets	No change in pain in challenge phase Decrease in NRS pain score subgroup analysis by 1.27 ($p=0.0439$). No significant decreases in pain intensity with daily home diary entries (-0.47, $p=0.0198$)	1
90	Neuropathic pain: MS	Nabilone	Average VAS _{pain} during the final 10 days of the trial was significantly lower in the Nabilone versus the placebo group ($p<0.001$); however, VAS _{intensity} scores were not significant ($p=0.77$). 100% of intervention group noted improvement in condition versus 43% placebo group.	1
91	Neuropathic pain	Sativex® oromucosal spray	NRS pain score reduced from 6.9 to 4.2 by the end of the study At least 50% of patients reported 30% improvement in pain at all times. 28% of patients were new responders at 30% level of improvement.	2
92	Neuropathic pain	Metered-dose inhaler (Δ^9 -THC)	Reduction of 3.4 points in VAS _{pain} scores ($p=0.001$) at 20 mins, return to baseline at 90 mins post-inhalation.	2
93	Chronic-non-cancer pain	Patient-dependent	Decrease in pain intensity in cannabis group versus control group; decrease sensory component of pain in cannabis group versus control group.	2
94	Chronic cancer chronic pancreatitis	non-pain: Single dose Namisol	Although there was a decrease in VAS _{pain} score there was a similar decrease in the active placebo group, and the results were not statistically significant.	2
95	Chronic cancer	non-pain: Namisol	Mean VAS _{pain} scores decreased by 1.6 and 1.9 in THC and placebo groups, respectively ($p=0.901$)	2

	chronic abdominal pain				
96	Chronic cancer functional pain	non-pain: chest	Dronabinol	Decrease in pain intensity and odynophagia after 28 days of treatment (p=0.04)	2
97	Cancer-related Pain		Nabilone	No significant decrease in VAS _{pain} between treatment and placebo groups.	2
98	Cancer-related pain		Patient-dependent (90% smoked)	70% of patients with prescription for medical marijuana indicated an improvement in pain control	3
99	Cancer-related pain: refractory	opioid	Sativex® oromucosal spray	Decrease in pain severity and worst pain scores at all time points versus placebo in long term study	2

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