Medical Cannabis Resource Guide
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About Tilray

Tilray is a Licensed Producer (LP) of medical cannabis in Canada. In April of 2014, we opened a 60,000 square foot cultivation, research and distribution center on Vancouver Island, British Columbia. This makes Tilray one of the world’s largest facilities dedicated to the production of medical cannabis.

Tilray’s mission is to become Canada’s leading producer of medical cannabis. Our staff includes PhDs, botanists and master horticulturists, all fully dedicated to providing healthcare practitioners and their patients with only the best products and services.

We are actively engaged in research—internally and in partnership with other academic institutions and laboratories worldwide—to advance the body of knowledge concerning cannabis and its use as medicine. We acknowledge that a significant amount of evidence supporting medical cannabis is anecdotal. However, combined with a growing body of clinically viable evidence confirming medical cannabis’ efficacy, the great magnitude of such evidence strongly supports continued, robust research.

It is important to note that, while hundreds of thousands of patients have reported obtaining relief from the use of cannabis, no evidence has come forth indicating significant toxicity. This fact has led to more and more healthcare practitioners recommending medical cannabis to their patients. Medical use of cannabis is legal in Canada, as well as Austria, the Czech Republic, Finland, Germany, Israel, Italy, the Netherlands, Portugal and Spain. As of this writing, medical use has been regulated in over 25 states in the United States.

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About Medical Cannabis

Medical cannabis is receiving increasing consideration as an effective therapy in the treatment of some diseases and alleviation of symptoms. While synthesized cannabinoids have been legally available for many years, use of the whole cannabis flower and cannabis extracts is only recently gaining greater acceptance, largely due to increasing evidence that such use can be a safe and effective adjunct or alternative to traditional pharmaceuticals.

Some members of the medical community have been tentative regarding the authorization of cannabis. However, research is being advanced in nations such as Canada, the US and Israel, and hundreds of thousands of patients worldwide have experimented with medical cannabis with a remarkably large percentage reporting positive effects. Increasingly, this anecdotal evidence is being corroborated by results of clinical research. At this stage, medical use of cannabis has shown potential efficacy in treating the following conditions or symptoms:

- Alcohol and opioid withdrawal symptoms (drug withdrawal symptoms) ¹
- Alzheimer’s disease, dementia ²
- Arthritis and musculoskeletal disorders (osteoarthritis, rheumatoid arthritis, fibromyalgia, osteoporosis) ³
- Cachexia (wasting syndrome) and loss of appetite in AIDS and cancer patients and anorexia nervosa ⁴
- Cancer ⁵
- Chronic pain ⁶
- Diseases of the pancreas (diabetes, pancreatitis) ⁷
- Epilepsy ⁸
- Gastrointestinal system disorders (Crohn’s disease, irritable bowel syndrome, inflammatory bowel disease, pancreatitis, metabolic syndrome/obesity, ulcerative colitis) ⁹
- Glaucoma ¹⁰
- Headache and migraine¹¹
- Hepatitis C and diseases of the liver (fibrosis, steatosis, ischemia-reperfusion injury, hepatic encephalopathy) ¹²
- HIV/AIDS ¹³
Hypertension 14

Inflammation 15

Inflammatory skin diseases (dermatitis, psoriasis, pruritus) 16

Metabolic syndrome 17

Movement disorders (dystonia, Huntington’s disease, Parkinson’s disease, Tourette syndrome) 18

Multiple sclerosis 19

Nausea and vomiting 20

Obesity 21

Palliative care (relief from pain and other distressing symptoms, and the enhancement of quality of life) 22

Post-operative pain 23

Psychiatric disorders (anxiety and depression, sleep disorder, post-traumatic stress disorder (PTSD)) 24


Why Tilray?

Selection
Tilray lets healthcare practitioners and patients choose from one the widest and varied strain selections in the industry. This ensures that patients will find the strains that best address their symptoms.

Supply
Healthcare practitioners and patients expect and deserve only the best service and products. Accordingly, we provide expedited delivery, prompt follow-up and consistent quality of each product we offer.

Research
We actively partner with leading scientists, academic institutions, healthcare practitioners, botanists and master horticulturists to build the body of knowledge about medical cannabis.

e-Portal
Tilray’s secure online e-portal allows physicians to easily and quickly manage patient records, receive patient feedback and issue authorizations. It facilitates the verification process so patients can place an order within minutes of their medical document being verified. In addition, the portal keeps the physician updated on events and educational information.

We’ve also introduced faxed medical documents to expedite the patient approval process. The new fax form is available on our website. The healthcare practitioner will be responsible for retaining a copy of the medical document in their records.

Tilray Assurance Program
Part of our ongoing commitment to improving the patient experience, the Tilray Assurance Program was created specifically for patients who do not have insurance coverage for medical cannabis. It offers patient credits for new registrations and renewals, along with senior and compassionate pricing programs.

Support
Support is available to physicians and patients 24 hours a day, 7 days a week. Tilray is the sole LP offering round-the-clock support. Our support team can be reached at 1-844-TILRAY1 (845-7291) or by email at tilray@tilray.ca.
An Introduction to THC and CBD

Medical cannabis contains hundreds of different chemical and pharmacological components.

Cannabinoids, the primary therapeutic chemical components in cannabis, are found in leaves and flowering tops of plants. There are over 100 cannabinoids identified in the cannabis plant, of which at least five are psychoactive. The two most studied and best understood cannabinoids are:

1. **Delta-9-tetrahydrocannabinol (THC)**

2. **Cannabidiol (CBD)**

The ratio of THC to CBD appears to play a large role in determining the therapeutic effects of cannabis. The concentration of each of these two cannabinoids depends on the plant strain and the conditions in which the plant was grown.

THC is the component in cannabis responsible for the psychoactive effects or “high” felt from cannabis. It has also been shown to be responsible for the immunosuppressive, anti-inflammatory and analgesic properties of cannabis.

CBD is the second most prevalent cannabinoid after THC. Research has shown that CBD produces a physical effect without the psychoactive effects associated with THC. CBD is thought to be responsible for anti-inflammatory, analgesic, anti-nausea, anti-emetic, anti-psychotic, anti-ischemic, anxiolytic, and anti-epileptic effects of cannabis.

Since the concentration of THC and CBD determines some of the potential health benefits and possible side effects of medical cannabis, a consistent THC-to-CBD ratio ensures that patients receive the cannabinoid concentration that has been shown to be beneficial for them. Furthermore, there is evidence CBD and THC work together to produce a synergy of effects and regulate each other. For instance, CBD may block anxiety provoked by THC.

“Cannabidiol (CBD), one major non-psychotomimetic compound of the Cannabis sativa plant, has shown anxiolytic effects in both humans and in animals.”

- **M. M. Bergamaschi et al.**

“Cannabinoid drugs can modulate the production of cytokines, which are central to inflammatory processes in the body.”

- **Janet E. Joy et al.**
1 to 1.25 grams per day is the average use rate by Canadian patients as reported by Health Canada at the 2014 Canadian Consortium for the Investigation of Cannabinoids (CCIC) conference in Toronto.

0.5 to 1.5 grams is the average daily dried flower cannabis use rate reported from medical cannabis programs in the Netherlands and Israel.³

For healthcare practitioners comfortable with the dosing of medical cannabis, our registration process gives you greater control over your patient’s course of treatment. In other cases, our team can work with you and your patients to determine the best strain and dose for optimal symptom management.


Medical cannabis legislation

Health Canada’s new regulations, the Marihuana for Medical Purposes Regulations (MMPR), came into effect on April 1, 2014. The new system allows the production and distribution of medical cannabis products (including whole flowers, oils, and capsules) by licensed producers overseen by Health Canada.

Health care practitioners (i.e. physicians and certain nurse practitioners) are able to authorize use of medical cannabis without any special training or licenses. Patients who apply to Tilray for medical cannabis must submit an application form and medical document signed by their health care practitioner. This application process can be completed by mail or through Tilray’s e-portal service.

All licensed producers under the MMPR must produce, process, and package medical cannabis in secure facilities like the one Tilray operates in Nanaimo, British Columbia. These facilities are regularly audited for compliance with applicable regulations.

Storefront distribution is not permitted under the MMPR. Instead, medical cannabis shipments are sent by secure courier. Patients have the option to receive their cannabis at their personal residence or at their healthcare practitioner’s office, with the healthcare practitioner’s consent.

The MMPR can be viewed in full at: http://www.laws-lois.justice.gc.ca/eng/regulations/SOR-2013-119/
Delivery Methods

There are three primary methods for administering cannabis: smoking, vaporization and ingestion. Physicians may want to consult with their patients to determine the preferred mode of delivery.

Cannabis must be heated to a temperature of 160-185°C in order for a process called decarboxylation to occur to the cannabinoids in the cannabis plant. Specifically, decarboxylation converts the tetrahydrocannabinolic acid (THCA) contained in dried cannabis into tetrahydrocannabinol (THC), and the cannabidiolic acid (CBDCA) into cannabidiol (CBD).

**Smoking and vaporization** offer the benefits of rapid onset of effect and ease of dose titration, which may be important for patients seeking fast symptom relief. Whereas smoking requires the burning of cannabis (typically using a pipe or cigarette), vaporization utilizes a device (vaporizer or nebulizer) that heats the cannabis to a temperature high enough to trigger decarboxylation and release cannabinoids as vapour, but too low to ignite or burn the cannabis. The vapour is then inhaled. Vaporization may be preferred by those concerned with the potential risks and irritation associated with smoking.1, 2 Relative to smoking, vaporization is practically odourless.

**Oral consumption** offers patients an application method that bypasses the pulmonary system entirely. While the effects of inhalation of cannabis smoke or vapour are nearly immediate and typically last two to four hours, the onset of effects from orally ingested cannabis (e.g., drops, sprays, capsules) is 60 to 90 minutes, and effects can last from eight to twelve hours.3 To achieve a comparable concentration of THC in the bloodstream, the dosage for orally ingested cannabis needs to be increased approximately 2.5 times4, 5 relative to smoking or vaporization.

“[A]n oral dose of 20 mg Delta9-THC would be approximately equivalent to a “smoked dose” of 8 mg of Delta9-THC.”3

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3. For further details, see the Health Canada publication Information for Health Care Professionals: Cannabis and the cannabinoids (February 2013) at http://www.hc-sc.gc.ca/dhp-mps/marihuana/med/infoprof-eng.php, which discusses cannabis intake via oral ingestion, vaporization, smoking, and topical application. Note that Tilray does not currently offer edible forms of cannabis or endorse their use, since the sale and possession of cannabis derivatives is currently prohibited under Canadian law. Although courts have found that patients are entitled to possess and consume cannabis derivatives in certain cases (see R. v. Smith, 2012 BCSC 544 and 2014 BCCA 322), this case is being considered by the Supreme Court of Canada. Physicians, patients, and caregivers are advised to check the judicial status and legal risks associated with creating and possessing cannabis derivatives (including edibles) before proceeding.


Current Applications

Contemporary research suggests cannabis may alleviate symptoms of a wide range of medical conditions. The following is a list of the most prominent current applications:

Arthritis

In the first-ever controlled trial of a cannabis-based medicine (Sativex) in the treatment of pain due to rheumatoid arthritis, a significant analgesic effect was observed. Compared to a placebo, the patients administered cannabis reported significant improvements in pain and quality of sleep.¹

“The spinal cord is loaded with cannabinoid receptors. These cannabinoid compounds [from marijuana] apparently reduce swelling from inflammation [a major symptom of arthritis]. But more than that, they kill the pain from inflammation specifically. They work on the peripheral nerves that carry pain from your joint into the spinal cord.”²

- J. Michael Walker, PhD

“Studies from chronic cannabis smokers have provided much of the evidence for immunomodulatory [modifying or regulating the immune system] effects of cannabis in humans...Cannabinoids can modulate both the function and secretion of cytokines [regulatory proteins] from immune cells. Therefore, cannabinoids may be considered for treatment of inflammatory disease.”³

- J. Ludovic Croxford

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Cancer

Lack of appetite and attendant weight loss are symptoms commonly experienced by those diagnosed with cancer.\textsuperscript{1, 2} Cannabis has long been associated with stimulating appetite,\textsuperscript{3} and pre-clinical studies show a correspondence between cannabis application and improvements in appetite, along with modest weight gain in some cancer patients.\textsuperscript{4, 5, 6}

Cannabis has been shown to be an effective analgesic and its use can be combined with opioids without significantly altering plasma opioid levels.\textsuperscript{7, 8}

Perhaps most interesting, a body of evidence is building indicating a correlation between application of cannabis and the inhibition of tumour growth.\textsuperscript{9, 10, 11} One study has indicated THC and CBD work together to slow tumour growth more effectively than when they are applied individually.\textsuperscript{12}

"Those treated with both irradiation and the cannabinoids saw the most beneficial results and a drastic reduction in size. In some cases, the tumours effectively disappeared in the animals."\textsuperscript{11}

-- Dr. Wai Liu et al.

"Delta(9)-THC and cannabidiol acted synergistically to inhibit cell proliferation. The treatment of glioblastoma cells with both compounds led to significant modulations of the cell cycle and induction of reactive oxygen species and apoptosis as well as specific modulations of extracellular signal-regulated kinase and caspase activities."\textsuperscript{12}

- J. P. Marcu et al.

"Delta(9)-tetrahydrocannabinol inhibited tumour-cell proliferation in vitro and decreased tumour-cell Ki67 immunostaining when administered to two patients."\textsuperscript{13}

- M. Guzmán et al.


**Chronic pain**

A large and growing body of clinical and anecdotal evidence supports the efficacy of cannabis as an analgesic.\textsuperscript{1,2,3,4} Unlike other common pharmaceutical analgesics, there appears to be no risk of overdose.\textsuperscript{5}

Cannabis has been shown to interact with endocannabinoid receptors, unique from those activated by opioids. Accordingly, cannabis can supplement the use of opioids\textsuperscript{5,6,7} and studies show an improvement in pain relief with patients taking morphine and oxycodone when their treatment was supplemented with vaporized cannabis.\textsuperscript{8}

Reports indicate that cannabis reduced pain and improved sleep patterns of patients suffering from post-traumatic or postsurgical pain.\textsuperscript{1}

Reported side effects of cannabis include but are not limited to: sedation, confusion, dizziness, anxiety, dry eyes and dry mouth. The degree of side effects may be dependent on quantity of dose and strain of cannabis.\textsuperscript{9}

“[I]t is difficult to compare studies of interventions for chronic pain with studies of experimentally-induced pain because of fundamental differences in the physiological state of the subjects, differences in the stimulus conditions and experimental protocols employed in the studies, and differences in the outcomes which are measured.”\textsuperscript{6}

- **Health Canada**

“Pharmacokinetic investigations revealed no significant change in the area under the plasma concentration-time curves for either morphine or oxycodone after exposure to cannabis. Pain was significantly decreased (average 27\%, 95\% confidence interval (CI) 9, 46) after the addition of vaporized cannabis.”\textsuperscript{8}

- D. I. Abrams et al.

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Crohn’s disease and ulcerative colitis

Evidence from pre-clinical trials and clinical studies indicates cannabis may have some effectiveness in treating inflammatory bowel disease (IBD) symptoms such as abdominal pain, diarrhea and inflammation. Again, correlation with the body’s endocannabinoid system is proposed as a factor. Animal testing has shown a slowing of weight loss, reduction of colon inflammation and a significant decrease in macroscopic damage.

Studies on human subjects have compelled researchers to urge further investigation of the efficacy of cannabis in the treatment of colitis and Crohn's disease. Significantly, subjects report improvements in quality of life, relating to their ability to perform daily activities and maintain a social life.

“THC was the most effective drug. The effects of these phytocannabinoids were additive, and CBD increased some effects of an ineffective THC dose to the level of an effective one. THC alone and in combination with CBD protected cholinergic nerves whereas sulphasalazine did not.”

- J. M. Jamontt

“The results indicate that cannabis may have a positive effect on disease activity, as reflected by reduction in disease activity index and in the need for other drugs and surgery. Prospective placebo-controlled studies are warranted to fully evaluate the efficacy and side effects of cannabis in CD.”

- T. Naftali et al.

“Three months' treatment with inhaled cannabis improves quality of life measurements, disease activity index, and causes weight gain and rise in BMI in long-standing IBD patients.”

- A. Lahat et al.

Epilepsy

The causes of epilepsy remain unknown in about half of all cases. However, recent discoveries have revealed an intercellular signalling system involving the brain's cannabinoid receptors. Activation of these receptors has been implicated in helping to explain the anticonvulsant properties of cannabinoids.  

Cannabidiol (CBD), which along with THC is the cannabinoid currently receiving the most attention for medical applications, has shown particular promise in reducing the frequency and severity of seizures. CBD has the added advantage of having minimal psychoactive effects, which may facilitate treatment for children.

“Preliminary, uncontrolled clinical studies suggest that cannabidiol may have antiepileptic effects in humans.”

- E. Gordon

“The concept that the endogenous cannabinoid system is activated on demand suggests that a promising strategy to alleviate seizure frequency is the enhancement of endocannabinoid levels by inhibiting the cellular uptake and the degradation of these endogenous compounds.”

- B. Lutz


Glaucoma

Evidence supporting the application of cannabis in treating glaucoma goes back to 1971, when Hepler and Frank reported a 25% to 30% reduction in intraocular pressure (IOP) among a small group that had smoked cannabis.\(^1\) It has been proposed that cannabis may activate receptors in the endocannabinoid system of the eye. (Decreased levels of endocannabinoids have been observed in glaucoma patients post-mortem.\(^2\)) Subsequent clinical testing has confirmed that application of cannabinoids reduces IOP, but that effects are relatively short in duration.\(^3\)

While the exact mechanism causing the pressure reduction has not yet been confirmed,\(^4\) it has been proposed that a reduction of capillary pressure, decreased aqueous humour production and improved aqueous humour uveoscleral outflow may be involved.\(^5, 6, 7, 8\)

“Aside from lowering IOP, cannabinoids such as \(\Delta\)-THC and CBD may also have neuroprotective effects which could also be useful in the management of glaucoma.”\(^3\)

- Health Canada


**HIV/AIDS**

Application of cannabis has been found to increase daily caloric intake and body weight in patients with AIDS, while improving mood and sleep.\(^1,\text{2}\) It has also been shown to relieve nausea and vomiting,\(^3\) and provide a significant decrease in pain.\(^4,\text{5}\) Patients have also reported a reduction in anxiety and relief from depression.\(^6\)

“Patients who smoked marijuana experienced 70-100% relief from nausea and vomiting, while those who used the THC capsule experienced 76-88% relief.”\(^3\)

–**Richard E. Musty et al.**

“As compared with placebo, cannabis and dronabinol dose dependently increased daily caloric intake and body weight in HIV-positive cannabis smokers... Effects of cannabis and dronabinol were comparable, except that only cannabis (3.9% THC) improved ratings of sleep.”\(^1\)

–**M. Haney**

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**Multiple Sclerosis**

Studies support the effectiveness of cannabis in treating a number of symptoms associated with MS, including pain and muscle spasticity. In addition, patients have reported improvement in quality of life when treated with the cannabinoid derivative, dronabinol.

Animal studies reveal, “THC has been shown to inhibit both clinical and histologic experimental autoimmune encephalomyelitis (EAE), it may prove to be a new and relatively innocuous agent for the treatment of immune-mediated diseases.”

“Smoked cannabis was superior to placebo in symptom and pain reduction in participants with treatment-resistant spasticity.”

*J. Corey-Bloom et al.*

“Oral dronabinol reduced central pain in patients with multiple sclerosis. Spontaneous pain intensity was reduced and pain relief was higher during dronabinol treatment than during placebo treatment, pressure evoked pain tended to decrease, and the patients tended to score better in the bodily pain domain of the health related quality of life questionnaire.”

*K. B. Svendsen et al.*

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Health Canada’s Information for Health Care Professionals: Cannabis (marihuana, marijuana, cannabis) and the cannabinoids reviews existing academic research into the application of cannabinoids for different conditions. For the complete Health Canada document, please visit:


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