Medical Cannabis and Gastrointestinal Disorders

An Overview for Healthcare Professionals

2018

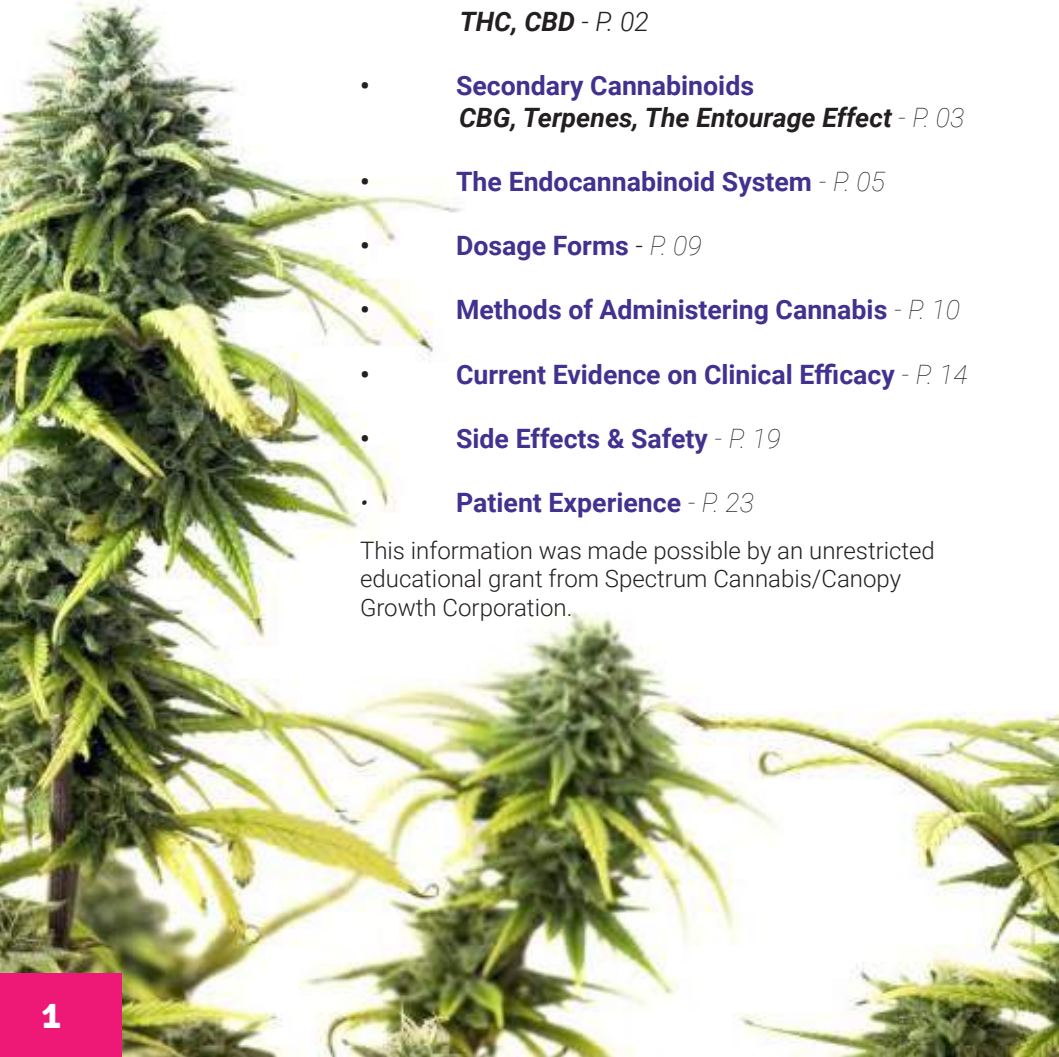
Introduction:

The use of medicinal preparations of cannabis can be traced back over five thousand years, making it one of the oldest medicinal plants (ElSohly 2002). This guide provides the necessary simplified information for medical professionals to make an informed decision about whether, and how, to incorporate medical cannabis into their patients' care.

Table of Contents:

- **Science of Cannabinoids**
  THC, CBD - *P. 02*
- **Secondary Cannabinoids**
  CBG, Terpenes, The Entourage Effect - *P. 03*
- **The Endocannabinoid System** - *P. 05*
- **Dosage Forms** - *P. 09*
- **Methods of Administering Cannabis** - *P. 10*
- **Current Evidence on Clinical Efficacy** - *P. 14*
- **Side Effects & Safety** - *P. 19*
- **Patient Experience** - *P. 23*

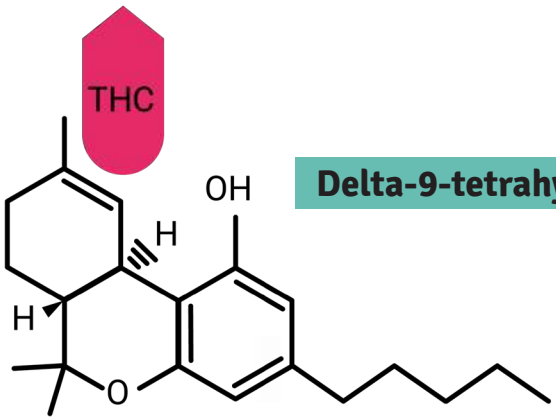
This information was made possible by an unrestricted educational grant from Spectrum Cannabis/Canopy Growth Corporation.



Science of Cannabinoids

More than 500 natural compounds have been identified and isolated from *Cannabis sativa*, including the medically important cannabinoids, terpenes, flavonoids, and other non-cannabinoid constituents. These compounds are produced in high concentration in the glandular trichomes, which are the hair-like, resin-secreting glands found on the surface of female cannabis flowers (Clarke and Watson 2002; Elsohly and Gul 2014).

More than 100 cannabinoid molecules have been identified in the cannabis plant (ElSohly and Gul 2014). Many are produced in trace amounts and, as a result, have not received thorough investigation. The pharmacology of the more prevalent cannabinoids, delta-9 tetrahydrocannabinol (THC) and cannabidiol (CBD), has been well researched (Russo 2011).



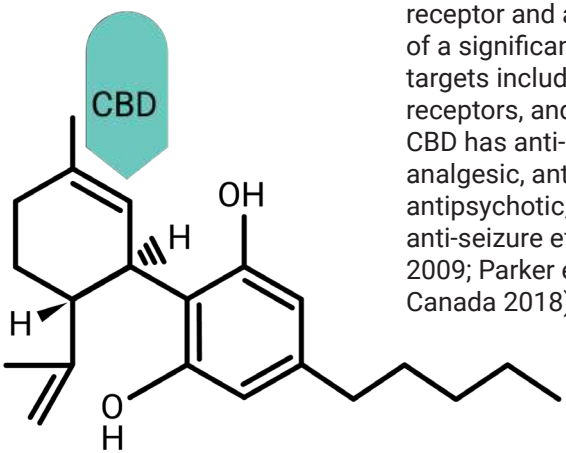
Delta-9-tetrahydrocannabinol

(THC)

THC is responsible for many of the pharmacological effects of cannabis, including the psychoactive effect. In addition to its well-known euphoric effects, THC interacts with cannabinoid receptors to induce analgesia, antispasmodic activity, reduction of chemotherapy induced nausea and vomiting, appetite stimulation, and decreased intestinal motility (Howlett et al. 2002; Grotenhermen and Müller-Vahl 2012; Health Canada 2018). Varieties with high concentrations of THC can cause anxiety, disorientation, and intoxication in some patients.

Cannabidiol (CBD)

CBD lacks the psychotropic effect of THC (ElSohly et al. 2013), although it has potential benefit as a treatment for anxiety disorders (Blessing et al. 2015). CBD has a low affinity for cannabinoid receptors (Thomas et al. 2007). It exerts indirect effects on the CB2 receptor and affects the activity of a significant number of other targets including ion channels, receptors, and enzymes.
CBD has anti-inflammatory, analgesic, antiemetic, antipsychotic, anxiolytic, and anti-seizure effects (Izzo et al. 2009; Parker et al. 2011; Health Canada 2018).



Secondary Cannabinoids

Medical cannabis contains a number of secondary cannabinoids for which there is limited evidence about effects. Many are precursors and metabolites of the primary active components, THC and CBD.

Cannabigerol (CBG)

Cannabigerolic acid (CBGA) is a precursor for both THC and CBD. CBG is commonly present in small amounts in cannabis, although some varieties have been bred to increase the proportion of CBG in the plant. CBG is a non-psychoactive cannabinoid that binds weakly to CB1 and CB2 receptors (ElSohly et al. 2013). In the lab, CBG inhibits the proliferation of keratinocytes and may have therapeutic potential in the treatment of psoriasis (Wilkinson and Williamson 2007).

Additional cannabinoids

Other cannabinoids that have drawn interest and attention due to their interaction with the endocannabinoid system include:

- Cannabinol (CBN)
- Cannabielsoin (CBE)
- Cannabinodiol (CBND)
- Cannabitriol (CBT)
- Cannabicyclol (CBL)
- Tetrahydrocannabivarin (THCV)

Terpenes

Terpenes are the primary aromatic compounds found in the essential oil of cannabis and are thought to be important active components. Like cannabinoids, terpenes are found in highest concentration in the resin produced by the flowers of female cannabis plants. Terpenes may have direct physiologic effects and may also interact with cannabinoids to create the unique effects of individual cannabis varieties (Russo 2011).

The Entourage Effect

The entourage effect is a theory that describes the potential interactions between major cannabinoids, minor cannabinoids, terpenes, and other plant constituents found in cannabis. Interactions between terpenes and cannabinoids may be responsible for experiences associated with particular varieties, such as those that make individuals feel sleepy after consumption or those that stimulate and encourage creativity (Russo 2011).

The Endocannabinoid System

The Endocannabinoid System (ECS) is a ubiquitous lipid signaling system present in all vertebrates and plays an important role in the regulation of homeostasis throughout the human body. It has been implicated in a broad range of physiological and pathophysiological processes, including neural development, immune function, inflammation, appetite, metabolism and energy homeostasis, cardiovascular function, digestion, bone development and bone density, synaptic plasticity and learning, pain, reproduction, psychiatric disease, psychomotor behaviour, memory, wake/sleep cycles, and the regulation of stress and emotional state (Health Canada 2018).

The ECS consists of endogenous receptors, ligands, and metabolic enzymes.

Receptors:

The cannabinoid receptors are G-protein coupled receptors (GPCR) named

1. Cannabinoid receptor 1 (CB1) and
2. Cannabinoid receptor 2 (CB2)

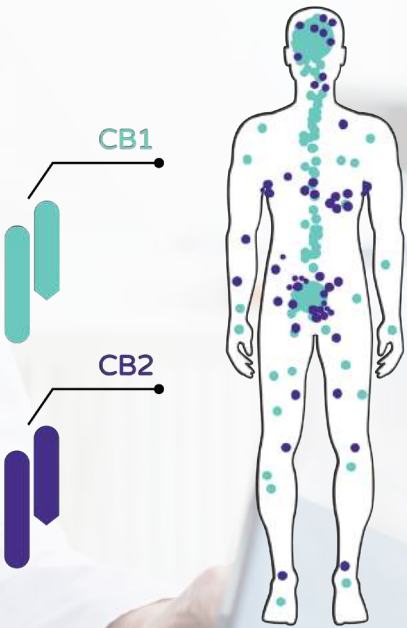
GPCRs are the largest and most diverse group of membrane receptors and include those controlling the adrenergic nervous system and many other ligand-receptor systems in all mammals (De Petrocellis et al. 2004).

CB1 Receptors:

The most abundant GPCRs in the CNS and are found in the highest concentration in the central and peripheral nervous system and the gastrointestinal system.

CB2 Receptors:

Found primarily in the immune system, including the tonsils, spleen, lymph nodes, and circulating lymphocytes and neutrophils.



Cannabinoid receptors are located on cell surfaces throughout the body.

Ligands

Two endogenous agonists (ligands) to cannabinoid receptors (i.e., endocannabinoids) have been identified:anandamide (AEA) and 2-arachidonoylglycerol (2-AG). Anandamide is derived from the Sanskrit term 'ananda',which means bliss. AEA can reproduce the typical effects of THC, such as euphoria. In addition, endocannabinoid synthesizing (PLD and DGL) and degrading enzymes (FAAH and MAGL) are responsible for the regulation of endocannabinoid levels and, thus, activation of the receptors (Mechoulam and Hanus 2000; Health Canada 2018).

Receptor activation

Cannabinoid receptor activation initiates a signaling cascade with differing results depending on the type and location of the receptors. In the CNS, endocannabinoids are produced on demand in the post-synaptic terminal in response to cellular, tissue, and organ demands. Cannabinioids (both endogenous and exogenous) can work on many pathways and in a variety of mechanisms. One way is by binding to CB1 receptors located on the pre-synaptic terminal with the overall effect of suppressing neurotransmitter release (e.g., glutamate, GABA, dopamine, and cholecystokinin). This retrograde signaling mechanism allows for the regulation of neurotransmission in a precise spatiotemporal manner (ElSohly 2002). Phytocannabinoids provide benefits via complex interactions with other receptors and ion channels in addition to CB1 and CB2 activation. For example, CBD is an agonist of serotonin (5-HT1A) receptors (Russo et al. 2005) and TRPV1 (vanilloid) receptors (Bisogno et al. 2001).

A Note On Indica and Sativa (Varieties)

Indica and sativa are used in plant taxonomy as species names and refer to the phenotype of a cannabis plant. These names are commonly used by medical cannabis patients, though there is disagreement about the validity of these distinctions. Recent analyses of cannabis varieties have found that, although the genetic makeup of varieties referred to as indica or sativa was moderately correlated to their reported ancestry, the names can be misleading. Even if *C. indica* and *C. sativa* are two distinct species, it would be rare to find a pure indica or sativa variety due to centuries of crossbreeding. Instead, the majority of cannabis varieties today are hybrids, created by crossbreeding two varieties, that may be indica or sativa dominant.

Some individuals believe that sativa varieties tend to be energizing and indica more sedating. When someone asks if a variety is sativa or indica, they want to know if the product will make them feel energized, and therefore good for daytime use, or sleepy, and therefore more suited to evening use.

Dosage Forms:

Dried Flowers

Dried cannabis is typically offered as either dried whole flowers (“bud”) or milled (“prepared” or “ground”). Whole flowers from the female cannabis plant are harvested, the stem and leaves are trimmed, and then the flowers are dried to a specific moisture content. Milled cannabis contains the same active ingredients as dried whole flowers and is ready for use in a vaporizer.

Cannabis Oil

Concentrated cannabis resin, containing cannabinoids and other active compounds, is extracted from cannabis flowers that have undergone thermal decarboxylation to make a product for your patients to take orally from a syringe. This allows them to know exactly how much THC and CBD they are consuming with each dose.

Softgels

Softgels are filled with cannabis resin dissolved in food-grade carrier oil. They offer patients a convenient and discreet option for their medication. Softgels may only be available from certain licensed producers of cannabis.

Methods of Administration:

It's important to understand the differences between inhaled and ingested methods of cannabis administration. It is also essential to choose the right method of administration, depending on a patient's symptoms and preferences. Some patients will require a combination, e.g., using cannabis oil to control baseline symptoms and inhaled cannabis for breakthrough symptoms.

Ways of using	When effects could begin	How long effects could last
Smoking/vaporizing	Seconds to minutes	Up to 6 hours*
Swallowing (food/ capsules)	30 minutes – 1.5 hours	Up to 12 hours*
Under the tongue	5-30 minutes	Up to 12 hours*

*some effects could last as long as 24 hours

Inhaled		Ingested
	ONSET	
5 -10 minutes		1- 3 hours
	DURATION	
2 - 4 hours		6 - 8 hours
	STARTING DOSE	
1 inhalation of dried flowers		2.5 mg of THC and equal amount CBD
	HOW IT'S ABSORBED	
through the lungs directly into the bloodstream		from the GI tract and metabolized in the liver before entering the bloodstream

Vaporizing

Vaporizing is a way to inhale the bioactive components of medical cannabis without burning the plant material. Cannabis is heated to a temperature that volatilizes, without combusting, the cannabinoids and other plant constituents, substantially reducing toxic by-products. In addition to reducing harm associated with smoking, vaporizing is a more efficient way of extracting the chemically active constituents from cannabis (Gieringer 2001; Gieringer et al. 2004; Hazekamp et al. 2006; Abrams et al. 2007; Pomahacova et al. 2009). It also reduces the loss of cannabinoids in sidestream smoke, which occurs in smoking. This leads to a substantial cost saving over smoking.

How vaporizing works

Typically, a small amount of ground cannabis flower is placed into a chamber in which the cannabis is progressively heated past the boiling point of its bioactive components, but not high enough to cause combustion. The vapors are either collected in a secondary chamber or directly inhaled, resulting in little product loss to the environment when compared with smoking. Patients should read and follow the instructions that come with the vaporizer they purchase. Some recommend to finely grind the flowers while others use a coarser grind. A small grinder can be used by the patient to prepare the cannabis to ensure best results.

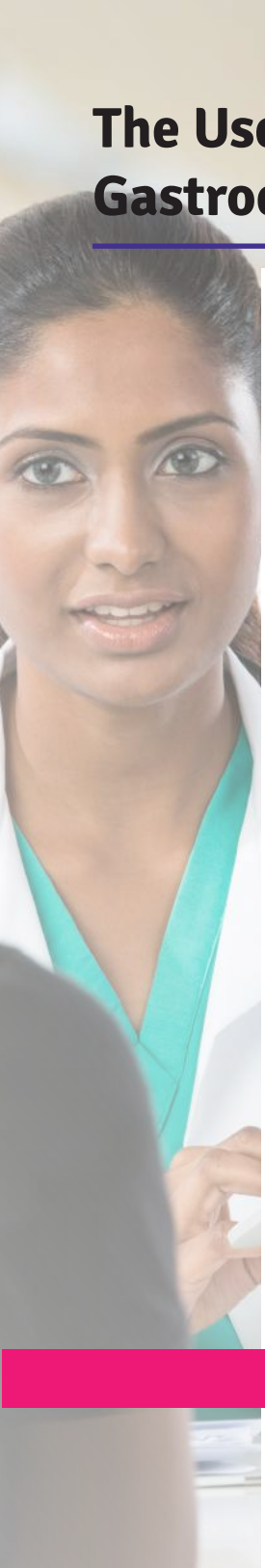
The long-term safety of inhaled cannabis vapor has not been studied, but may be a safer, more efficient and effective alternative to the known harms of smoking (Russo and Hohmann 2013). A summary of the literature suggests that vaporizers might prevent pulmonary problems associated with smoking (Loffin and Earleywine 2015).

Vaporizers vary in size, portability, battery life, warranty, and customizability of temperature settings and mouthpieces. Portability is especially pertinent since patients using the larger devices, such as the Volcano, which is not portable, may resort to smoking cannabis cigarettes (joints) when they are not at home. Some vaporizers have been tested and registered as medical devices.

Ingestion

Ingesting cannabis oil from an oral dosing syringe or in softgels ensures accurate dosing. It is not recommended to add oil to baked goods or other food (e.g., yogurt) as dosing precision is lost.

The Use of Medical Cannabis in Gastroenterology



Research into the therapeutic efficacy of cannabis, its extracts, and refined phytochemicals has been an active area of study for over 40 years and is accompanied by a vast amount of anecdotal evidence and case reports of therapeutic benefit. The list of conditions that medical cannabis is alleged to treat continues to grow, but research is still lacking in many areas.

Although many patients report that it alleviates their symptoms, it remains unclear whether cannabis and its extracts are effective for treating GI conditions. Two major limitations to designing proper clinical studies are regulatory licensing hurdles and the lack of development and supply of a true placebo.

Despite a lack of high-quality evidence due to regulations, some research indicates that medical cannabis may improve GI conditions such as severe nausea, inflammatory bowel disease (IBD), and chronic pain.

Inflammatory Bowel Disease (IBD)

There is currently a large unmet need in the treatment of IBD with conventional medical therapy. Despite improvement in disease activity, many patients have persistent clinical symptoms that have significant impact on their quality of life. Patients have been seeking out alternative therapies (including cannabis) to help manage persistent symptoms associated with IBD (Kinnucan, 2018).

Surveys of cannabis use in IBD patients in the United States and Canada have found that approximately 15% to 20% of patients currently use cannabis, and up to 40% have tried cannabis to relieve IBD symptoms.

These retrospective studies have shown that many IBD patients report cannabis improves symptoms such as pain, appetite, and diarrhea. In these studies, patients have used cannabis by both oral an inhalation routes (Kinnucan, 2018)

Crohn's Disease

A small study was designed to determine if cannabis (smoked) could induce remissions in Crohn's disease patients who were unresponsive to steroids, immunomodulators, or anti-TNF agents (Naftali et al. 2013). Clinical response was seen in 10 of 11 patients in the cannabis group compared to 4 in 10 in the placebo group. Three patients in the cannabis group were weaned from steroid dependency. Those receiving cannabis had improved appetite and sleep and no significant side effects.

Recently, in the first study of its kind, cannabis oil has been shown to significantly improve the symptoms of Crohn's disease and the quality of life sufferers but, contrary to previous medical thinking, has no effect on gut inflammation (Naftali, et al. 2018).

In this randomized, placebo-controlled study, researchers from Israel have shown that cannabis can produce clinical remission in up to 65% of individuals after 8 weeks of treatment, but that this improvement does not appear to result from a dampening down of the underlying inflammatory process. Going forward, the research group plans to explore the potential anti-inflammatory properties of cannabis in the treatment of IBD further.

Recently, Dr. Naftali stated "There are very good grounds to believe that the endocannabinoid system is a potential therapeutic target in Crohn's disease and other gastrointestinal diseases... For now, however, we can only consider medicinal cannabis as an alternative or additional intervention that provides temporary symptom relief for some people with Crohn's disease.' (Naftali, et al. 2018)

Ulcerative Colitis

Irving and colleagues (2018) assessed the efficacy, safety, and tolerability of once-daily oral CBD-4% THC (CBD-rich extract) for 10 weeks in patients with active ulcerative colitis (N=60) as an adjuvant therapy while on stable dosing of mesalamine therapy. Patients were less tolerant to the CBD-rich extract than placebo, and there were significant protocol deviations in the study. Both groups failed to reach the primary endpoint of clinical remission, and there were no differences in the rates of remission between the groups (28% for the CBD-rich extract and 26% for placebo). Per-protocol analysis showed improvement in patient's global impression of change and a trend toward improved quality-of-life scores with CBD-rich extract use.

Most recently, unpublished data were presented by Naftali and colleagues at the 2018 Digestive Disease Week. They evaluated the effects of smoking 2 cannabis (THC-rich) cigarettes daily or placebo for 8 weeks in patients with moderate to severe ulcerative colitis (N=28). In this study, medical cannabis use was associated with improved clinical disease activity scores and endoscopic improvement (reduction of Mayo endoscopic subscore from 2 to 1; $P < .01$). However, there was no significant change in CRP or fecal calprotectin in either group.

Other GI Disorders & Symptoms

The potential use of medical cannabis for pain management is also of great clinical interest. It is promising that vaporized cannabis augments the analgesic effects of opioids and cannabinoids and can reduce the dose of opioids used by chronic non-cancer patients (Lynch and Clark 2003; Abrams et al. 2011).

Further, it has been shown to help those with nausea and vomiting. For instance, a review of 28 studies that included 1,772 participants suffering from chemotherapy-induced nausea and vomiting found a greater benefit of cannabinoids for the treatment of nausea and vomiting than an active comparator or placebo (Whiting et al. 2015).

The evidence for treating irritable bowel syndrome (IBS) specifically is sparse at this time. We're beginning to see clinical experience suggesting effectiveness at reducing diarrhea and relieving abdominal pain, but more research is needed in this area.

Side Effects & Safety

While cannabis is safe on its own and has a relatively small chance of significant drug-drug interactions, it is recommended to monitor patients for clinical response to both cannabis and to other pharmaceuticals that could interact with cannabis.

Possible Side Effects	Most Common	Common	Rare
Drowsiness/fatigue	✓		
Dizziness	✓		
Dry mouth	✓		
Cough, phlegm, bronchitis (smoking only)	✓		
Anxiety	✓		
Nausea	✓		
Cognitive effects	✓		
Euphoria		✓	
Blurred vision		✓	
Headache		✓	
Orthostatic hyotension			✓
Toxic psychosis/paranoia			✓
Depression			✓
Ataxia/dyscoordination			✓
Tachycardia (after titration)			✓
Cannabis hyperemesis			✓
Diarrhea			✓

Chart Based on in vitro and animal studies with cannabis, there is a potential for interaction with the medications metabolized by the P450 enzymes (2C9, 2C19, 3A4).

Drugs that can increase THC levels include:

- antidepressants (e.g., fluoxetine, fluvoxamine)
- proton pump inhibitors (e.g., omeprazole)
- cimetidine
- macrolides (e.g., clarithromycin, erythromycin)
- antimycotics (e.g., itraconazole, fluconazole, ketoconazole, miconazole)
- calcium antagonists (e.g., diltiazem, verapamil)
- HIV protease inhibitors (e.g., ritonavir)
- amiodarone
- isoniazid

Drugs that may decrease the availability of THC include:

- rifampicin
- carbamazepine
- phenobarbital
- phenytoin
- primidone
- rifabutin
- St. John's wort

Many of these drug interactions can be mitigated in complex patients with polypharmacy by slowly titrating cannabis.

While most studies have concentrated on THC, CBD does have some notable drug-drug interactions, including increasing the blood levels of the anticonvulsant clobazam in children with refractory epilepsy (Geffrey et al. 2015). These drugs should be used together very cautiously and clinicians are strongly encouraged to refer to medical experts.

Monitoring patients for clinical response to cannabis, in addition to monitoring for response to other pharmaceutical agents that could interact with cannabis (e.g., for hypertension management continue to monitor blood pressure) is recommended. More research is clearly needed in this area. Please report any adverse event or drug interaction to Health Canada.

While cannabis is safe on its own and has a relatively small chance of significant drug-drug interactions, it can have an additive effect when added to other CNS depressants. For this reason, patients currently taking benzodiazepines, hypnotics, or opioids should be monitored closely and consideration to start at a lower dose should be made.

For more information on drug interactions refer to Health Canada's Information for Health Care Professionals: Cannabis (marihuana, marijuana) and the cannabinoids

Disclaimer: Physicians who choose to authorize cannabis for their patients must comply with their provincial or territorial regulatory College's relevant guideline or policy.

Patient Experience

JASON'S STORY

37 yrs, diagnosed with ulcerative colitis at 20

I had become dependent on steroids to stay in remission and had two operations to remove my colon and create a pelvic pouch. I was still having symptoms years after and decided to try cannabis, which some people I know with the disease had tried.

Experience at the Clinic:

I went through a private clinic, but I also let my doctor know. I was very nervous about bringing it up to him, but he was supportive and helpful. Telling him was actually a great thing because it opened me up with being honest with doctors about it, which is important. For example, if I go to the ER I tell them I use cannabis because it affects how they sedate me, if they need to. Cannabis helps me through pain, so if I am prescribed a narcotic I often reject the prescription because cannabis is enough for me. Doctors are impressed and happy by this.

The clinic I went to was amazing! Very supportive, clean and the environment was professional in nature.

Method of Use:

My preffered method is smoking, sometimes I vape or use edibles. Smoking is most effective for me. I have tried oils, pills but they are not my preference, and don't help as much. Smoking/vaping gives me almost instant relief. Other methods take a while to kick in and affect me differently.

Side Effects:

In the begining I was worried about side effects. I hated it in high school and was worried about not being in control of my actions or it causing worse problems. I actually find now that I am older and more mature, I can control my actions and my intake without needing to get silly high.

A Note on Safety:

I don't drive with it. I consider it the same as alcohol and treat it as such. I keep it away from my work life and use cannabis when I am not at work, or doing work. Otherwise, I feel that since it can have an impairment factor, I use it away from doing things involving kids, work, driving, etc.

Advice for Others:

It is worth trying it – I was always against it but I took a risk and it does work. When using it, however, you must exercise responsibility and treat it like alcohol because there can be an impairment factor. Start with a small dose to see how it affects you, increase small and slowly. Good luck!

References:

Abrams DI, Vizoso HP, Shade SB, Jay, C. et al. 2007. Vaporization as a Smokeless Cannabis Delivery System: A Pilot Study. Clin Pharmacol Ther. 82:572-578.

Abrams DI, Couey P, Shade SB, Kelley ME, Benowitz NL. 2011. *Cannabinoid-opioid interaction in chronic pain*. Clin Pharmacol Ther. 90(6):844-851.

Bisogno T, et al. 2001. Molecular targets for cannabidiol and its synthetic analogues: effect on vanilloid VR1 receptors and on the cellular uptake and enzymatic hydrolysis of anandamide. Br J Pharmacol. 134:845-852.

Blessing EM, Steenkamp MM, Manzanares J, Marmar CR. 2015. Cannabidiol as a potential treatmet for anxiety disorders. Neurotherapeutics. 12(4):825-836.

Clarke RC, Watson DP. 2002. Botany of Natural Cannabis Medicines. In: Cannabis and Cannabinoids – Pharmacology, Toxicology, and Therapeutic Potential. The Haworth Press; p. 3-13.

De Petrocellis L, Cascio MG, Di Marzo V. 2004. The endocannabioid system: a general view and latest additions. Br J Pharmacol. 141(5):765-7745.

ElSohly M. 2002. Chemical Constituents of Cannabis. In: Cannabis and Cannabinoids – Pharmacology, Toxicology, and Therapeutic Potential. The Haworth Press; p. 27-36.

Elsohly M, Gul W. Constituents of Cannabis Sativa. 2014. In: Handbook of Cannabis. Oxford University Press; p. 3-22.

ElSohly M, Upton R, Craker L, et al. 2013. Cannabis inflorescence, cannabis spp.; standards of identity, analysis, and quality control. American Herbal Pharmacopoeia (AHP).

Geffrey AL, Pollack SF, Bruno PL, Thiele EA. 2015. Drug-drug interaction between clobazam and cannabidiol in children with refractory epilepsy. Epilepsia. 56(8):1245-1251.

Gieringer DH. 2001. Cannabis Vaporization. J Cannabis Therapeutics. 1:153-170.

Gieringer D, St Laurent J, Goodrich S. 2004. Cannabis vaporizer combines efficient delivery of THC with effective suppression of pyrolytic compounds. J Cannabis Therapeutics. 4:7-27.

Grotenhermen F, Müller-Vahl K. 2012. The therapeutic potential of cannabis and cannabinoids. Dtsch Arztebl Int. 109(29-30):495-501.

Hazekamp A, Ruhaak R, Zuurman L, et al. 2006. Evaluation of a vaporizing device (Volcano) for the pulmonary administration of tetrahydrocannabinol. J Pharm Sci. 95:1308-1317.

Health Canada. 2018. Information for Health Care Professionals: Cannabis (marihuana, marijuana) and the cannabinoids. Government of Canada. https://www.canada.ca/en/health-canada/services/drugs-medication/cannabis/information-medical-practitioners/information-health-care-professionals-cannabis-cannabinoids.html. Published 2018. Accessed October 26, 2018.

Howlett AC, Bonner BF, Cabral G, et al. 2002. International Union of Pharmacology. XXXVII. Classification of cannabinoid receptors. Pharmacol Rev. 54(2):161-202.

Irving PM, Iqbal T, Nwokolo C, et al. A randomized, double-blind, placebo controlled,
parallel-group, pilot study of cannabidiol-rich botanical extract in the symptomatic treatment of ulcerative colitis. Inflamm Bowel Dis. 2018;24(4): 714-724.

Izzo AA, Borrelli F, Capasso R, Di Marzo V, Mechoulam R. 2009. Non-psychotropic plant cannabinoids: new therapeutic opportunities from the ancient herb. Trends Pharmacol Sci. 30(10):515-527.

Kinnucan J., MD. (2018). *Use of Medical Cannabis in Patients With Inflammatory Bowel Disease.* Retrieved October 30, 2018, from http://www.gastroenterologyandhepatology.net/archives/october-2018/use-of-medical-cannabis-in-patients-with-inflammatory-bowel-disease/

Loffin M, Earleywine M. 2015. No smoke, no fire: what the initial literature suggests regarding vapourized cannabis and respiratory risk. Can J Respir Ther. 51(1):7-9.

Lynch ME, Clark AJ. 2003. *Cannabis reduces opioid dose in the treatment of chronic non-cancer pain.* J Pain Symptom Manag. 25(6):496-498.

Mechoulam R, Hanus L. 2000. A historical overview of chemical research on cannabinoids. Chem Phys Lipids. 109(1-2):1-13.

Naftali T, Bar-Lev Schlieder L, Konikoff F, et al. *Cannabis induces clinical response but no endoscopic response in Crohn's disease patients*. Presented at UEG Week Vienna 2018, October 22, 2018.

Naftali T, Schleider LBL, Dotan I, et al. 2013. Cannabis induces a clinical response in patients with Crohn's disease: a prospective placebo-controlled study. Clin Gastroenterol and Hepatol. 11(10):1276-1280.

Parker L, Rock EM, Limebeer CL. 2011. Regulation of nausea and vomiting by cannabinoids. Br J Pharmacol. 163(7):1411-1422.

Pomahacova B, Van der Kooy F, Verpoorte R. 2009. Cannabis smoke condensate III: the cannabinoid content of vaporised Cannabis sativa. Inhal Toxicol. 21:1108-1112.

Russo EB, Burnett A, Hall B, Parker KK. 2005. Agonistic properties of cannabidiol at 5-HT1a receptors. Neurochem Res. 30:1037-1043.

Russo E. 2011. Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects. Br J Pharmacol. 163(7):1344-1364.

Russo EB, Hohmann AG. 2013. Role of cannabinoids in pain management. In: Deer TR, et al., ed. Comprehensive Treatment of Chronic Pain by Medical, Interventional, and Integrative Approaches. http://www.springer.com/gp/book/9781461415596. p.181-197. Accessed December 1, 2017.

Thomas A, Baillie GL, Phillips AM, Razdan RK, Ross RA, Pertwee RG. 2007. Cannabidiol displays unexpectedly high potency as an antagonist of CB1 and CB2 receptor agonists in vitro. Br J Pharmacol. 150:613-623.

Whiting PF, Wolff RF, Deshpande S, et al. 2015. *Cannabinoids for medical use: a systematic review and meta-analysis.* JAMA. 313(24):2456-2473.

Wilkinson JD, Williamson EM. 2007. Cannabinoids inhibit human keratinocyte proliferation through a non-CB1/CB2 mechanism and have a potential therapeutic value in the treatment of psoriasis. J Dermatol Sci. 45:87-92.

Canadian Digestive Health Foundation

For more information, visit CDHF.ca.

CDHF is the official Foundation of the Canadian Association of Gastroenterology. We are directly connected to Canada's leading digestive health experts, physicians, scientists and other health care professionals. You can trust us to provide you with practical, science-based information that is up to date and unbiased.

This information was made possible by an unrestricted educational grant from:
Spectrum Cannabis/Canopy Growth Corporation

SpectrumCannabis™

CANOPY GROWTH CORPORATION