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EVERYTHING ABOUT THC

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Consultant physician at Santé Cannabis

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DISCLOSURE

- The Prescriber Training Program is supported by an unrestricted educational grant provided by Spectrum Therapeutics
- Funding facilitates the program offered free-of-charge to all Quebec physicians
- No service fees for patients to access shared-care education service
- Santé Cannabis is identified as a Contractual Research Organization (CRO) and collaborates with select companies (pharma industry) in research consultations and clinical trials

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DISCLOSURE

Dr Alain Watier is:

- A speaker on Cannabis for Therapeutic Purposes
  (physicians, pharmacists, nurses, trainees in medicine and pharmacy)
- Member of the advisory committee for cannabis for therapeutic purposes:
  Canopy Growth Corporation, Tilray, Aurora
- Conferences subsidized by licensed medical cannabis producers
- Author of webinars on the subject

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EVERYTHING ABOUT THC

OVERVIEW

- THC
- ENDOCANNABINOID SYSTEM
- EFFECTS OF THC
- PHARMACOKINETICS
- OTHER USEFUL INFORMATION

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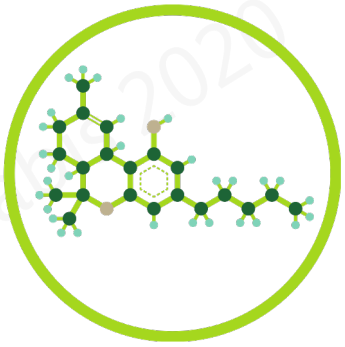
Δ-9-TETRAHYDROCANNABINOL (THC)

- Highly lipophilic molecule
- Main psychoactive cannabinoid found in cannabis
- 15 to 30% THC in the cannabis plant
- Sought after for its psychoactive effects - recreational use
- High level of THC in cannabis both a challenge and opportunity for therapeutic use



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PHARMACEUTICAL CANNABINOIDS

Two pharmaceutical products with similar pharmacology to THC:

1 - NABILONE (CESAMET™):

- **Synthetic THC analogue** tablet/syrup
- Indicated for chemotherapy-related nausea/vomiting
- May help to relieve pain and improve sleep
- Available in Canada
- Currently the only cannabinoid therapy covered by the RAMQ (certain formats)

- Valeant Canada limited. 2009. "PRODUCT MONOGRAPH Cesamet Nabilone." https://pdf.hres.ca/dpd_pm/00007760.PDF.

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PHARMACEUTICAL CANNABINOIDS

Two pharmaceutical products with similar pharmacology to THC :

2 – DRONABINOL (MARINOL™):

- **Synthetic THC** tablet/syrup
- Indicated for chemotherapy-related nausea/vomiting
- Indicated for the treatment of anorexia in patients with HIV/AIDS.
- May help to relieve pain and improve sleep
- Not available in Canada

• AbbVie Inc. 2017. "MARINOL (Dronabinol) Capsules, for Oral Use," 20.

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THE ENDOCANNABINOID SYSTEM

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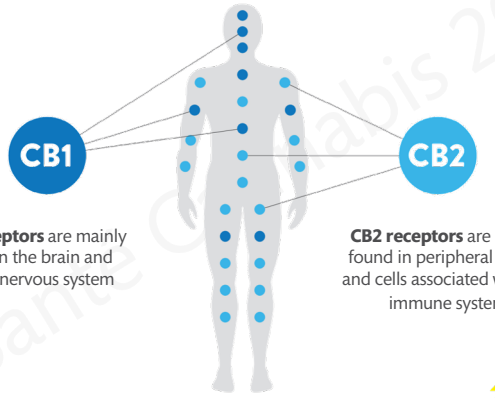
THE ENDOCANNABINOID SYSTEM

2 main receptors of the endocannabinoid system:



CB1 receptors are mainly found in the brain and central nervous system

CB2 receptors are mainly found in peripheral organs and cells associated with the immune system

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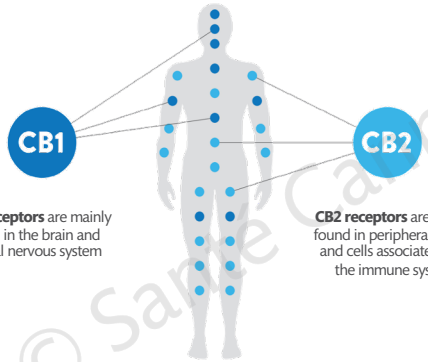
THE ENDOCANNABINOID SYSTEM

2 main receptors of the endocannabinoid system:



CB1 receptors are mainly found in the brain and central nervous system

CB2 receptors are mainly found in peripheral organs and cells associated with the immune system

***Δ*-9-Tetrahydrocannabinol (THC)**

Partial agonist of receptors CB1 and CB2

= effects on multiple systems

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THC

Effects related to the endocannabinoid system

Effects	CB1 receptor	CB2 receptor
Euphoric/intoxicant	x	
Analgesic	x	x
Anti-emetic	x	
Anti-spasmodic	x	
Appetite stimulant	x	x
Sedative	x	
Anti-inflammatory		x
Anxiolytic (biphasic)	x	
Neuroprotective	x	

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EFFECTS OF THC

[Natural THC, Dronabinol and Nabilone]

- Therapeutic effects
- Side effects
- Precautions

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MAIN THERAPEUTIC EFFECTS

Supported by moderate to high scientific evidence

- **ANTI-EMETICS**
- **ANALGESIC**
- **ANTI-SPASMODIC**
- **SEDATIVE**
- **APPETITE STIMULANT**

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THC'S THERAPEUTICAL EFFECTS

1- Anti-emetics

- Effective for the treatment of **chemotherapy-induced nausea and vomiting**
- Level of evidence on effectiveness: conclusive

→ Inhibits 5-HT3 receptors
→ Interacts with CB1 receptors

→ **Efficacy superior to metoclopramide, chlorpromazine, thiethylperazine, haloperidol, domperidone or alizapride**

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THC'S THERAPEUTICAL EFFECTS

2- Analgesics

- Reduces **chronic** and **neuropathic pain**
- Level of evidence on effectiveness: conclusive

→ Cumulative and synergic analgesia with **opioids**

→ Not effective for acute pain

→ Analgesic effect mediated by CB1 and CB2 receptors

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THC'S THERAPEUTICAL EFFECTS

3- Anti-spasmodic

- Reduction of muscle spasticity, particularly associated with multiple sclerosis
- Level of evidence on effectiveness: conclusive

→ Result of the interaction with CB1 receptors

→ Anti-spasmodic effect linked to THC

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THC'S THERAPEUTICAL EFFECTS

4- Sedative/Sleep modulator

- Promotes **sleep**
- Level of evidence on effectiveness: Moderate

- Reduces sleep problems such as **insomnia** or **sleep disturbance**
- Reduces **nightmares** and insomnia caused by **post-traumatic stress disorder**

→ Results from the interaction with CB1 receptor
→ Increases Slow Wave Sleep
→ Decreases Rapid Eye Movement (REM) Sleep

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THC'S THERAPEUTICAL EFFECTS

5- Appetite Stimulant

- Could increase the incentive value of food and the motivation to ingest appetizing foods
- Helps **stabilize** or **gain weight**
- Level of evidence on effectiveness : Moderate

→ Several studies in patients with cancer, HIV/AIDS, Alzheimer's disease and anorexia
→ Effect on appetite could involve receptors CB1 and CB2
→ Potential effect of THC on Leptin/Ghrelin levels

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OTHER POSSIBLE THERAPEUTIC USES

Insufficient evidence

- MOVEMENT DISORDERS
- GASTROINTESTINAL DISORDERS
- ANXIETY AND FEAR
- ALZHEIMER'S DISEASE
- GLAUCOMA
- ASTHMA

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OTHER POSSIBLE THERAPEUTIC USES

THC could also have potentially beneficial effects in other medical applications;
More studies are needed to support these indications.

Movement disorders

- May be effective to reduce tics and behavioural problems - Tourette's Syndrome

Gastrointestinal disorders

- THC decreases digestive motility at large
- Irritable Bowel Syndrome and Cannabis
- Cannabis and Inflammatory Bowel Diseases
  - Reduction of disease activity index
  - Does not affect the physiopathology but improves the symptoms

→ Presence of CB1 receptors in the colon

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OTHER POSSIBLE THERAPEUTIC USES

THC could also have potentially beneficial effects in other medical applications;
More studies are needed to support these indications.

Anxiety and fear

- May be effective to relieve some anxiety disorders (phobias and post-traumatic stress disorder)
- THC could help with fear extinction

Alzheimer's disease

- Could decrease agitation and aggressive behavior
- Possible role in slowing the progression of the disease
- Probable necessity of CBD in the treatment plan

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OTHER POSSIBLE THERAPEUTIC USES

THC could also have potentially beneficial effects in other medical applications;
More studies are needed to support these indications.

Glaucoma

- Could decrease intraocular pressure
- Effects with multiple routes of administration (oral, inhalation or topical)

Asthma

- Bronchodilation with inhaled THC; anti-inflammatory effects
- But smoked cannabis can also cause
  - Bronchial constriction
  - Allergies
  - Respiratory tract irritation

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SIDE EFFECTS & PRECAUTIONS

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THC'S SIDE EFFECTS

Most common	Occasional	Rare
Sedation	Euphoria	Extreme Anxiety
Sleepiness	Vasodilatation	Panic attacks
Fatigue	Headache	Depression
Dry mouth	Hypotension	Tachycardia
Anxiety	Nausea	Ataxia
Cognitive effects	Dizziness	Psychosis
	Diplopia	Hyperemesis

*Individual and dose-dependent response

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PRECAUTIONS WITH THC

Schizophrenia and psychosis

THC can:

- Induce psychosis
- Worsen schizophrenia

Precautions:

- Avoid THC in patients with a personal or family history of schizophrenia.
- Avoid THC in patients with a history of psychosis
- Avoid THC in patients under 25 years old

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PRECAUTIONS WITH THC

Cardiovascular function

Consumption of THC can cause

- Tachycardia
- Increased blood pressure (especially at initiation)
- Peripheral vasodilation, causing in turn:
  - → decrease in blood pressure
  - → minor orthostatic modifications

Precautions:

- Avoid or limit THC for patients with
  - Uncontrolled hypertension
  - Ischemic heart disease
  - Other active unstable cardiac conditions

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PRECAUTIONS WITH THC

Dependence

THC causes addiction

→ Abuse potential for plant-based, synthetic and synthetic analogue of THC

→ As opposed to CBD, which shows no potential for abuse [W.H.O.]

→ 2-9%: Prevalence of lifelong cannabis dependence in occasional recreational users

→ 30-50% of daily recreational cannabis users might develop cannabis dependence

→ Data on **recreational** cannabis (pre-legalization population studies)

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PRECAUTIONS WITH THC

Dependence

Precautions:

- Harm reduction approach
- Limit THC consumption
- Control administration (dose format)
  - Consider oral administration
  - Avoid smoking
  - Avoid vapourization of THC-rich cannabis
- Beware of risk factors related to the development of a substance use disorder:
  - Early initiation to cannabis (young age), sex (male), history of substance abuse, childhood sexual abuse, psychosocial factors

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PRECAUTIONS WITH THC

Long-term side effects - effects on the brain

- Importance of THC/CBD ratio
- High THC ratio could increase the potential for harms

Precautions:

- Special consideration for patients under 25 years of age

→ Avoid or limit THC

→ Control dosage and format

Necessity of medical supervision

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PHARMACOKINETICS

- Absorption
- Distribution
- Metabolism
- Excretion

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THC PHARMACOKINETICS

Administration methods for medical cannabis:

- **Oral**
- **By Inhalation**

Most frequent methods of administration

- **Oromucosal** (transmucosal)
- **Topic**
- **Rectal**

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THC PHARMACOKINETICS

Oral

- Slow absorption in the intestinal tract + metabolism by the liver
- 4-20% bioavailability only (synthetic and natural THC)
- Onset of effects in 1-3 hours
- Effects lasting 6-8 hours

→ Comparable to long-acting drugs

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THC PHARMACOKINETICS

By Inhalation

Smoked or with a **vapourizer**

- Rapid absorption through the lungs
- Avoids metabolism by the liver
- 10-35% bioavailability
- Onset of effects in 5-10min
- Effects lasting 2-4 hours

→ Comparable to short-acting drugs

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THC PHARMACOKINETICS

Oromucosal (transmucosal)

- Absorption through oral mucosa - rapid/intermediate

→ E.g. with Nabiximols/Sativex™ (THC 27mg/mL + CBD 25mg/mL)

- Avoids metabolism by the liver
- Onset of effects in 30min-1h
- Effects lasting 4-6 hours

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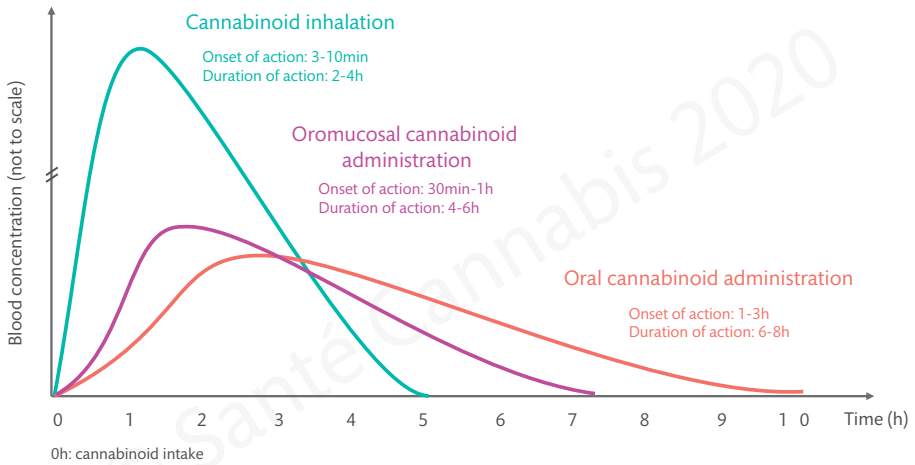
CANNABINOID ADMINISTRATION & ABSORPTION



Qualitative representation of cannabinoid absorption

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THC PHARMACOKINETICS

Other less frequent administration methods:

Topical

- Absorption through the skin
- Very lipophilic nature of THC limits its absorption by the skin (aqueous)
- Not as well characterized

Rectal

- Absorption through the rectal mucosa
- Pro-drug THC hemisuccinate is absorbed, not THC alone.
- Lower hepatic metabolism → improved bioavailability
- Onset of effects in 1-2 hours,
- Effects lasting 6-8 hours

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THC PHARMACOKINETICS

Distribution

- rapid in vascularized tissues (lungs, heart, liver, brain)
- bound to plasma proteins
- **THC = highly lipophilic**
- Accumulation in adipose tissue, liver, lungs, pancreas

→ especially with chronic use

- Crosses the placental barrier
- Also found in breast milk

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THC PHARMACOKINETICS

Metabolism

- Mainly **hepatic**, by cytochrome P450 enzymes :
  - CYP 2C9, CYP 2C19 and CYP 3A4
- Caution with drugs that inhibit these enzymes

→ e.g. proton pump inhibitors, macrolides, azole antifungals, some antidepressants, ...

- THC also inhibits the action of certain CYP450 enzymes

THC → 11-OH-THC (active) → 11-COOH-THC (inactive)

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THC PHARMACOKINETICS

Excretion

- Feces (over 65%)
- Urine (about 20%)
- THC also found in sweat, saliva and hair.

- Half-life of THC :
  - 1 to 3 days for light users
  - from 5 to 13 days for heavy users

→ Long half-life due to accumulation in adipose tissue

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PHARMACODYNAMIC INTERACTIONS WITH THC

The use of THC may increase sedation and cognitive impairment in patients who use THC concurrently:

- Alcohol
- Opioids
- Antipsychotics
- Benzodiazepines
- Tricyclic antidepressants
- Anticonvulsants

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OTHER USEFUL INFORMATION

+ MYTHS AND PRECONCEPTION ABOUT THC

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OTHER USEFUL INFORMATION

In the patient naïve to medical cannabis,
THC is taken by slow, progressive
and conservative titration

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OTHER USEFUL INFORMATION

THC and driving

Quebec: zero-tolerance

Canada

- THC limit (road test): less than 2 nanograms/mL of blood

→ 2-5 ng THC = lesser offence (maximum 1000$ fine)

→ 5 ng THC et plus = more serious offence (minimum of 1000$ fine)

Limit THC + Alcohol:

- 50 mg or more of alcohol per 100 ml of blood and 2.5 ng or more of THC per ml of blood (minimum of 1000$ fine)

Testing:

- No road test - Blood sample needed
- Physical coordination tests to determine if there is impairment

Government of Canada, Department of Justice. 2018. "Impaired Driving Laws." June 22, 2018. https://www.justice.gc.ca/eng/cj-jp/sidl-rlcfa/.

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OTHER USEFUL INFORMATION

THC and work

- Using cannabis for medical purposes is a right
- Patients are encouraged to be transparent with their employer
- Patients should avoid any potentially dangerous work (driving, using heavy machinery, etc.) when taking THC

Necessity of individualized support regarding work-place and other impairment challenges

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MYTHS & PRECONCEPTION ABOUT THC

Patients want cannabis/THC for the "high" or euphoria

In general, that is false.

- In clinical care, intoxication is considered an adverse event or side effect
- Patients are often afraid or suspicious of THC
- Patients often have no desire to smoke cannabis
- Dissociative effect of THC can be beneficial (pain perception, PTSD, Anxiety)

[From Santé Cannabis' experience]

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MYTHS & PRECONCEPTION ABOUT THC

One can't overdose on cannabis/THC

In practice, it is very unlikely to consume sufficient doses of cannabis/THC to cause a lethal overdose.

- The calculated lethal dose in a 70kg human would be approximately 4g of pure THC
- Upper limit of recommended THC doses (Santé Cannabis): 50mg/day

According to the WHO, low THC mortality reflects the low density of CB1 receptors in areas of the brain stem that control vital cardiovascular or respiratory functions

World Health Organization. 2018. "WHO Expert Committee on Drug Dependence Pre-Review." https://www.who.int/medicines/access/controlled-substances/Section3-thc-Toxicology.pdf?ua=1.

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MYTHS & PRECONCEPTION ABOUT THC

One can't overdose on cannabis/THC

However, it is possible to take too great a dose (non-lethal overdose) of THC

- resulting in adverse events and unwanted side effects

Especially:

→ when unsupervised (or recreational use)

→ dosage uncontrolled

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MYTHS & PRECONCEPTION ABOUT THC

One can get intoxicated by eating cannabis raw flowers or leaves

False.
Fresh cannabis flowers and leaves contain little or no Δ9-THC.

- The acid form (THCA) found in the raw plant is not psychoactive

- THC = Decarboxylated form of THCA
- Decarboxylation occurs as a result of heating (mainly) or exposure to light (to a lesser extent)

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CONCLUSION

- **THC has several uses in modern medicine**
- **Like any other medication, it is not indicated for every disease – conditions or symptoms must be carefully considered**
- **There is still considerable acquisition and transmission of scientific and clinical knowledge needed concerning THC and medical cannabis**

For more information on medical cannabis, Santé Cannabis developed a Prescriber Training Program.

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PRESCRIBER TRAINING PROGRAM

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TRAINING OFFERINGS

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- Self-learning online modules that detail treatment evidence for specific conditions and symptoms.
- Practical reference guidebook on developing and managing treatment plans and dosing.
- Clinical Toolkit to help navigate patient assessment and follow-ups.
- Clinical preceptorships opportunities with Santé Cannabis
- Nurse visit to your practice site for assessment and follow-up of your patients

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Medical cannabis doesn't have to feel like uncharted territory anymore.

SUPPORT SERVICE OFFERINGS

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- **Shared-care services**
  - education session for your patients at one of our clinics or by phone to review treatment modalities and product options.
- **Ongoing personalized phone and email support** for all questions about cannabis for medical purposes

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