

Cannabis: State of the evidence for appropriate medical use

Editorial note

- Evidence of the potential risks and benefits of the use of cannabis for therapeutic purposes is limited to mostly small, observational studies, and many of the effects are still unknown.
- While a few synthetic cannabinoid products have been approved for clinical use, cannabis has not been approved for use as a medicine for any indication by Health Canada or the U.S. Food and Drug Administration. Cannabis has not gone through the regulatory processes required to be approved as a pharmaceutical product as a result of limited evidence supporting its safety and effectiveness.

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What is cannabis

- Cannabis contains over 70 active compounds known as cannabinoids, each of which can have a different effect on the body, specifically the brain and central nervous system.
 - The most common cannabinoids are delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). THC is the primary ingredient that causes psychoactive ("high") effects. CBD may produce therapeutic effects but does not cause psychoactive effects.
 - Depending on the type of cannabis plant and preparation, either THC or CBD is the most abundant cannabinoid.

How does it work?

Cannabinoids

- **Cannabinoids** are similar to certain naturally occurring compounds in the body, in particular in the brain, known as endocannabinoids.

- An example of an endocannabinoid is anandamide, a compound naturally produced by the body that has effects similar to those of THC.

- The **endocannabinoid** system has important regulatory functions and may have a role in controlling various physiological and pathophysiological processes.

- Endocannabinoids, such as anandamide, and cannabinoids, such as THC and CBD, **activate certain receptors** in the body. Different receptor types appear to play different roles in human physiology. Currently, the two most well-known cannabinoid receptors include CB1 and CB2.

- CB1 receptors: found in the central and peripheral nervous systems, they are responsible for the psychoactive effects of THC and may play a role in memory, mood, sleep, appetite and pain.

- CB2 receptors: found predominantly in the cells of the immune system, they may play a role in reducing inflammation.

CADTH Evidence Driven.



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Indications and contraindications for use

Conditions that may benefit from cannabis use

● Evidence has shown cannabis has a potential benefit in the treatment of:

- 1 nausea and vomiting due to chemotherapy
- 2 chronic pain
- 3 spasticity and muscle spasms due to multiple sclerosis or paraplegia
- 4 sleep disorders
- 5 Tourette syndrome

● There is inconclusive evidence on the use of cannabis for the treatment of:

- 1 loss of appetite in patients with HIV/AIDS
- 2 anxiety disorders
- 3 glaucoma
- 4 epilepsy
- 5 Parkinson's disease
- 6 Alzheimer's disease or dementia
- 7 rheumatoid arthritis

Contraindications to cannabis use

● According to Health Canada Guidelines, cannabis should not be used in patients who:

- 1 are under the age of 25
- 2 are allergic to smoke or any cannabinoid
- 3 have serious liver, kidney, heart, or lung conditions
- 4 have a personal or family history of serious mental illness, such as schizophrenia, psychosis, depression, or bipolar disorder
- 5 have a history of alcohol or drug abuse or substance dependence
- 6 are planning to get pregnant, are pregnant, or are breast-feeding
- 7 are male and wish to start a family

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Health effects and harms

Interaction with other substances

The effects of cannabis can be increased if used with other substances, such as alcohol, blood thinners, nonsteroidal anti-inflammatories, opioids, sleep medications, or other psychoactive drugs.

Nabilone can cause additive central nervous system depressant effects when used in combination with diazepam, alcohol and codeine.

Nabilone combined with opioids can produce opioid-sparing effects and decrease the need for NSAIDs, TCAs, dexamethasone and ondansetron.

Second-hand cannabis smoke

Some of the harmful chemicals found in tobacco smoke are also found in cannabis smoke. Exposure to second-hand cannabis smoke can cause a positive THC urine test and psychoactive effects in those passively exposed, with the extent of second-hand effect depending on the environment (ventilation) and dosages (amount of THC in smoked cannabis and number of cigarettes smoked).

Tolerance, dependence, and addiction

The addictive potential of cannabinoids is considerably less than many other commonly abused prescription and illicit substances. Risk factors for addiction include:

- Early age of onset of cannabis use (under 25 years of age)
- High stress
- Presence of comorbid mental disorders
- History of substance abuse
- Experiencing a negative life event
- Peer use

The brain adapts to the presence of cannabinoids, which may lead to dependence and withdrawal if intake is stopped abruptly. Symptoms of withdrawal can include restlessness, irritability, agitation, hot flashes, sleep disturbance, nausea, and cramping.

- Symptoms of withdrawal are expected to be much milder and shorter-lived than those associated with opiates or other psychoactive drugs. The risk of dependence is also lower.
- Chronic use of cannabis can result in a reduced response or tolerance to it. Tolerance does not always indicate an addiction to or dependence on cannabis.

Health effects associated with cannabis use

	Increased risk of:	Inconclusive evidence on risk of:
Overall health	anxiety bloodshot eyes depression disorientation dizziness drowsiness dry mouth euphoria hallucinations headaches impaired mental functioning (e.g., concentration, memory) impaired motor skills (e.g., slower reaction time, muscle relaxation)	impaired pulmonary function low blood pressure nausea panic attacks paranoia rapid heart rate respiratory problems or worsening of existing lung conditions slowed digestion stroke vision problems weakened immune system worsening of seizures
Risk of cancer	testicular	bladder cervical childhood penile prostate
Mental health	mania neurological soft signs psychosis in general	relapse in patients with psychosis or schizophrenia anxiety depression psychosis in high-risk individuals suicide
Brain structure and chemistry	decreased global functioning decreased hippocampal volume	decreased levels of glutamate and dopamine impaired blood flow reduced white matter
Neurocognitive function	impaired memory reduced ability to feel pleasure reduced efficiency	
Pre- and post-natal health	birth complications childhood mental health problems such as inattention and impulsivity	low baby birth weight physical anomalies and defects

Health effects associated with cannabis use (*continues from previous page*)

Sub-populations at an increased risk of the harmful effects of cannabis

- 1 Pregnant women:** cannabinoids pass through the placenta and can slow the growth of a fetus.
- 2 Breast-feeding women:** cannabinoids pass into breast milk and can slow the development of a baby.
- 3 Children and adolescents:** during developmental periods, the brain is more vulnerable to the long-term health effects of cannabis. Cannabis use at an early age has been associated with reduced mental and emotional development. Cannabis use may also influence use of other illicit drugs in adolescents or in adults who started use at an early age.
- 4 Individuals with a personal or family history of psychosis:** cannabis use may increase the risk of experiencing psychosis or a worsening in existing psychosis.

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Route of administration and dosage

- Cannabis may be taken by mouth (consumed in edible products, such as baked goods or teas, or buccal/sublingually), inhaled (smoked or vaporized), inserted rectally (suppositories), and applied topically (gels, creams or patches).

Oral ingestion: cannabinoids are processed by the digestive tract and liver before being absorbed into the bloodstream (known as the first pass effect). The liver metabolizes THC into an additional potent psychoactive metabolite. Cannabis delivered buccally or sublingually is absorbed by the oral mucosa into the bloodstream, avoiding liver metabolism.

Inhalation: the extensive network of blood vessels in the lungs enables cannabinoids to be rapidly absorbed into the bloodstream without being metabolized by the liver. Therefore, less of the psychoactive metabolite seen after oral ingestion is produced. In comparison to smoking, vaporizing allows for greater absorption of THC and produces less toxic products (e.g., carbon monoxide, polycyclic aromatic hydrocarbons, and tar).

Rectal insertion: due to the large surface area available for absorption and reduced first pass metabolism, cannabis rectal suppositories may have a higher bioavailability. However, only certain forms of THC are absorbed via this route.

Topical application: while transdermal administration bypasses metabolism by the liver, the hydrophobic nature of cannabinoids limits their ability to be absorbed beyond the skin. There have been no clinical studies on cannabis gels or creams, and only animal studies on dermal patches.

	Onset of effects	Peak of effects	Duration of effects
Oral foods, tea and oral mucosal	30 minutes – 4 hours	1 – 6 hours Can have more than one peak	8 – 24 hours
Smoking and vaporization	Within 5 minutes	30 minutes	2 – 4 hours

Dosing recommendations

- Cannabis dosing is complex due to interindividual and pharmacological variables.
 - While rough guidelines for cannabis dosing exist, precise dosages for different routes of administration or specific medical conditions have not been established.

A dose of THC between 2.5mg and 3.0mg is associated with therapeutic benefit. Higher doses of THC are associated with an increased risk of adverse effects.

On average, a **typical joint** contains 0.5g to 1.0g of dried cannabis plant material and weighs 750mg, which may contain between 7.5mg (1%) and 225mg (30%) THC. Individuals typically use between 0.75mg and 3.2mg of THC from dried cannabis in smoked, vaped, and/or ingested form.

The actual amount of THC absorbed via inhalation, estimated to be around 25% of the total THC in a joint, is affected by how long a breath is held after inhaling and how many puffs are taken, making it difficult to give a precise dosage.

The dose of THC in oral form is equivalent to 2.5X the dose of THC in smoked form.

Dosing is highly individualized and requires assessment with titration. Patients with no previous experience should begin with a very low dose (e.g. 1mg THC), which can be increased gradually until the required effect, self-determined by the patient, is reached.

To give enough time to feel the full effects and limit overdosing, patients should **wait 30-60 minutes between bites** of oral products or a few minutes between inhalations.
 - **Guidelines** on the most appropriate CBD to THC dose ratio for different clinical indications **do not exist**.
- Limited evidence suggests:**
- When CBD is pre-administered, the effects of THC are potentiated. When CBD and THC are administered simultaneously, the effects of THC are potentiated if the CBD to THC ratio is around or less than 2 to 1 and the effects are attenuated when the CBD to THC ratio is at least 8 to 1.

Monitoring

In Alberta, physicians prescribing cannabis are recommended to:

- 1 **Get to know the patient well** prior to prescribing cannabis, to be aware of the presence of risk factors for dependence and addiction.
- 2 **See patients at least once every three months** to assess side effects, effectiveness, and misuse.
- 3 **Monitor patients at a higher risk of adverse effects**, such as patients with testicular cancer, functional brain changes, or mental health conditions, or pregnant and breast-feeding women, more closely.
- 4 **Complete a dependency risk assessment tool** for patients at increased risk of dependency.

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