# Safety: Contraindications, Adverse Events, Interactions, Cannabis Use Disorder





1

## Safety: Contraindications, Adverse Events, Interactions, Cannabis Use Disorder

- 1. Discuss contraindications, short-term and long-term potential adverse events arising from cannabis use
- 2. Identify potential pharmacokinetic and pharmacodymanic interactions between cannabis and medications
- 3. Identify signs of cannabis use disorder and describe tools to appropriate assess





## Is It Safe For Everyone To Take Cannabis?

#### Generally avoid using cannabis if patient: Use with caution if patient: a) Is under the age of 25 a) Has a concurrent active mood or anxiety disorder b) Has a personal history or strong family history of psychosis b) Smokes tobacco c) Has a current or past cannabis use disorder, or other substance use disorder c) Is heavy user of alcohol or taking high doses of opioids or benzodiazepines or other sedating d) Is pregnant, planning to become pregnant, or breastfeeding medications prescribed or available over the e) Has a known allergy to cannabis, THC, CBD or any other cannabinoid d) Has risk factors for cardiovascular disease f) Has cardiovascular disease g) Has respiratory disease

Cannabis may be used with caution in situations where evidence suggests that benefits outweigh risks

Authorizing Dried Cannabis for Chronic Pain or Anxiety, CFPC, September 2014 RXTx Ottawa (ON): Canadian Pharmacists Association; c2018. CPS online: Cannabis;





3

#### **Potential Short-term Adverse Effects**

#### **Neurocognitive / Central Nervous System**

- Drowsiness, dizziness, confusion
- Feeling "high" (euphoria, relaxation, distorted perception)
- Headache
- · Reduced attention, reactivity, problem solving, judgment
- Psychomotor impairment



Driving: Individuals who drive soon after consuming cannabis have a 2-fold higher risk of being involved in a motor-vehicle accident. Avoid driving for 4 hours after inhalation, 6 hours after oral ingestion

Elderly: May lead to increased falls

Volkow ND et al. Adverse Health Effects of Marijuana Use. N Engl J Med . 2014 June 5; 370(23): 2219–2227.
Canadian Pharmacist's Letter, Online Continuing Education. Medical Marijuana. Volume 2017, Course No. 231
Ware, M. et al. (2015). Cannabis for the Management of Pain: Assessment of Safety Study (COMPASS). The Journal of Pain, 1233-1242.
RxTx Ottawa (ON): Canadian Pharmacists Association; c2018. CPS online: Cannabis





## **Potential Short-term Adverse Effects**

Cardiovascular	Gastrointestinal
<ul> <li>Tachycardia</li> <li>Supine hypertension, postural/orthostatic hypotension</li> <li>Irregular heart rate and rhythm</li> <li>Peripheral vasodilation</li> </ul>	<ul> <li>Dry mouth</li> <li>Increased appetite</li> <li>Nausea, vomiting, constipation</li> <li>Decreased gastric emptying</li> </ul>
Increased blood pressure	Psychiatric
Increased risk of myocardial infarction or stroke	<ul><li>Acute psychosis</li><li>Hallucinations, anxiety</li></ul>

RxTx Ottawa (ON): Canadian Pharmacists Association; c2018. CPS online: Cannabis





5

## **Potential Long-term Adverse Effects**

Psychiatric	Reproductive
<ul> <li>Worsening or pre-existing anxiety/depression/bipolar</li> <li>Possible earlier onset of schizophrenia in youth</li> <li>Amotivational syndrome</li> </ul>	<ul> <li>Fetal exposure may result in lasting neurodevelopmental deficits</li> <li>Possible association with increased fetal loss, low birth weight, prematurity</li> </ul>
Cognitive	Gastrointestinal
Lower IQ in regular adolescent users	Cannabis Hyperemesis Syndrome (CHS)

RxTx Ottawa (ON): Canadian Pharmacists Association; c2018. CPS online: Cannabis





## **Potential Long-term Adverse Effects**

Specific to Smoking Cannabis		
Respiratory	Carcinogenic Effects?	
<ul> <li>Chronic bronchitis, cough, wheeze, sputum</li> <li>Increased rates of pneumonia</li> </ul>	<ul> <li>Smoke may contain many of the same chemicals as tobacco smoke</li> <li>Condensates may be more cytotoxic and mutagenic</li> </ul>	

Volkow ND, et al. N Engl J Med . 2014 June 5; 370(23): 2219–22270 Information for Health Care Professionals; Cannabis (marihuana, marijuana) and the cannabinoids, Health Canada 2018





7

## **How Common Are AEs?**

#### **Most Common**

- Drowsiness, fatigue
- Dizziness
- Dry mouth
- Cough, phlegm, bronchitis (smoking only)
- Anxiety
- Nausea
- Cognitive effects

#### Common

- Euphoria
- Blurred vision
- Headache

#### Rare

- Orthostatic hypotension
- Toxic psychosis/paranoia
- Depression
- Ataxia/dyscoordination
- Tachycardia
- Cannabis hyperemesis
- Diarrhea

MacCallum CA, Practical considerations in medical cannabis administration and dosing Eur J Internal Med 2018; 49:12-19





## **Tolerance**

Tolerance	Dependence
Defined as either:  • A need for markedly increased cannabis to	As manifested by either:  • The characteristic withdrawal syndrome for cannabis, or
achieve intoxication or desired effect, or  • A markedly diminished effect with	Cannabis taken to relieve or avoid withdrawal symptoms
continued use of the same amount of substance	With abrupt discontinuation:  • May result in irritability, restlessness, headache
Reversible after discontinuing cannabis	• Symptoms start in 1-2 days, peak in 2-6 days, finish by 2 weeks (but can last up to 4 weeks)
With chronic, high-dose use:  • Downregulation of CB-1 receptors	Limited evidence to guide dose tapering

Information for Health Care Professionals; Cannabis (marihuana, marijuana) and the cannabinoids, Health Canada October 2018 Bonnet U, Preuss UQ. The cananbis withdrawal syndrome 2017.





9

## **Cannabis Use Disorder (CUD)**

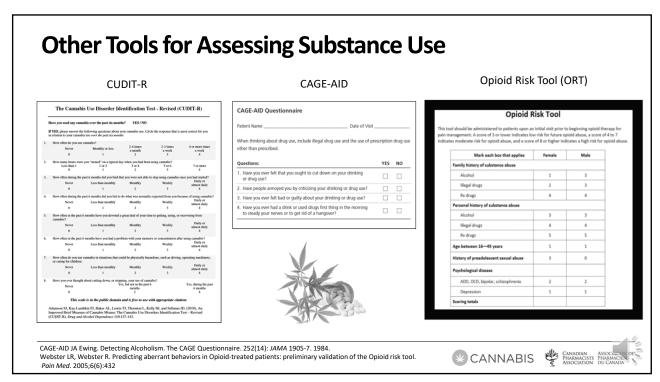
Definition	Signs it may be occurring
A problematic pattern of cannabis use leading to clinically significant impairment or distress	<ul> <li>Cannabis is taken in larger amounts or over a longer period than was intended</li> <li>Persistent desire or unsuccessful efforts to cut down or control use</li> <li>Craving/strong desire/urge to use cannabis</li> <li>Failure to fulfill work/school/home commitments</li> <li>Continued use despite harm to relationships</li> <li>Using in physically hazardous situations</li> <li>Some limited evidence that CBT and other forms of psychotherapy may help with CUD</li> </ul>

**Useful Tool: Cannabis Use Disorder Identification Test – Revised (CUDIT-R)** 

Adamson SJ et al. Drug and Alcohol Dependence 110:137-143.







11

### **Overdose**

- Cannabis or THC overdose can produce dose-dependant mental and physical effects
- Acute effects (e.g., panic attacks, psychosis, hallucinations, hyperemesis) managed with reassurance, quiet, administration of benzodiazepines, IV fluids
- Life threatening ventricular tachycardia has been reported
- No reports of fatal overdose
- Lethal dose of THC estimated to be more than 75,000 mg cannabis (more than even a very heavy user would consume in a day)

Information for Health Care Professionals; Cannabis (marihuana, marijuana) and the cannabinoids, Health Canada October 2018 🔟 CANNABIS RxTx Ottawa (ON): Canadian Pharmacists Association; c2018. CPS online: Cannabis





## **Drug-Drug Interactions**

#### **Pharmacokinetic**

- THC and CBD metabolized by CYP2C9, 2C19, 3A4
- CBD also metabolized by 1A2 and 2D6 and can inhibit 2C19, 2D6 and CYP3A4, also inhibits
- CBD inhibits metabolism of clobazam used in epileptic patients
- Smoked cannabis induces CYP1A2
- Increased risk of hepatotoxicity with CBD and VPA likely CYP mediated

#### **Pharmacodynamic**

• Potential for additive dizziness, drowsiness and sedation when taken with medications with similar AEs (e.g. opioids, BZDs, anticholinergic, antihypertensives)

Caution is warranted for ALL drugs that have a narrow therapeutic index Start low and go slow Many case reports of DDIs available





13

## **Drug Interactions**

Drug	Potential Interaction with Cannabis
Anticholinergics (e.g., amitriptyline, clozapine, nortriptyline, etc.)	Additive tachycardia and/or hypertension
CNS depressants (e.g., alcohol, barbiturates, benzodiazepines*, opioids, etc.)	Additive effects e.g. sedation, cognitive impairment)  *CBD can lead to enhanced active metabolite(s) of clobazam
CYP1A2 substrates (e.g., acetaminophen, amitriptyline, caffeine, clozapine, duloxetine, etc.)	Increased serum concentrations of these medications *Decreased serum concentrations of these medications if cannabis is smoked
CYP2C19 substrates (e.g., escitalopram, citalopram, omeprazole, sertraline, etc.)	Increased serum concentrations of these medications
CYP2C9 inhibitors (e.g., fluconazole, fluoxetine, miconazole, etc.)	Increased serum concentrations of cannabis
CYP3A4 inducers (e.g., carbamazepine, phenobarbital, phenytoin, rifampin, St. John's wort, etc.)	Reduced serum concentrations of cannabis
CYP3A4 inhibitors (e.g., azole antifungals), grapefruit juice, macrolides, etc.)	Increased serum concentrations of cannabis
Nicotine	Additive tachycardic and stimulant effects
Stimulants (e.g., amphetamines, ecstasy/MDMA)	Additive tachycardia Hyperthermic effects Increased risk of CNS impairment (long-term use)





## **How to Manage Potential Adverse Events?**

- Reduce frequency, potency, amount of dose
- Reduce amount of THC
- Or stop completely

#### Recognize:

- That tolerance can develop over weeks, months
- That withdrawal symptoms can occur
- The signs of problematic cannabis use

https://uwaterloo.ca/pharmacy/sites/ca.pharmacy/files/uploads/files/cannabis\_infographic\_bw.pdf





15

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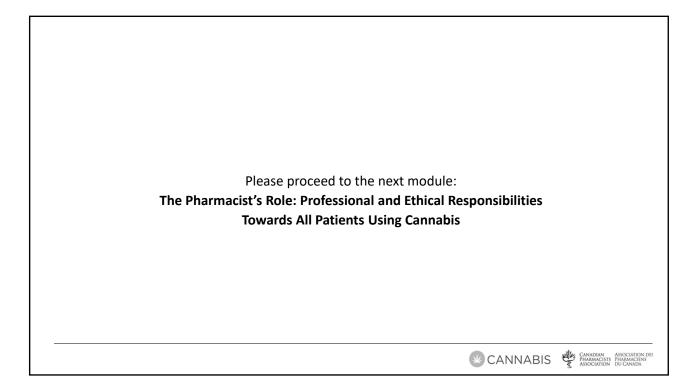




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17



18