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





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

Cannabis may be used with caution in situations where evidence suggests that benefits outweigh risks.
Consider using with caution in patients that are driving or operating heavy machinery, as it should be avoided after consumption of cannabis

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

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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, 8 hours if patient experiences euphoria after cannabis consumption

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

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Potential Short-term Adverse Effects

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

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

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Potential Long-term Adverse Effects

Psychiatric	Reproductive
• Worsening or pre-existing anxiety/depression/bipolar • Possible earlier onset of schizophrenia in youth • Amotivational syndrome	• Fetal exposure may result in lasting neurodevelopmental deficits • Possible association with increased fetal loss, low birth weight, prematurity • Low sperm count
Cognitive	**Gastrointestinal**
• Lower IQ in regular adolescent users • Cognitive decline/impairment	• 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?
• Chronic bronchitis, cough, wheeze, sputum • Increased rates of pneumonia	• Smoke may contain many of the same chemicals as tobacco smoke • Condensates may be more cytotoxic and mutagenic

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

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

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Tolerance

Tolerance	Dependence
Defined as either: • A need for markedly increased cannabis to achieve intoxication or desired effect, or • A markedly diminished effect with continued use of the same amount of substance • Reversible after discontinuing cannabis With chronic, high-dose use: • Downregulation of CB-1 receptors	As manifested by either: • The characteristic withdrawal syndrome for cannabis, or • Cannabis taken to relieve or avoid withdrawal symptoms With abrupt discontinuation: • May result in irritability, restlessness, headache, fever/chills, insomnia, anxiety and other symptoms • Symptoms start in 1-2 days, peak in 2-6 days, finish by 2 weeks (but can last up to 4 weeks) • 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.
RxTx Ottawa (ON): Canadian Pharmacists Association; c2018. CPS online: Cannabis

Cannabis Use Disorder (CUD)

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

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

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

Other Tools for Assessing Substance Use

CUDIT-R

The Cannabis Use Disorder Identification Test - Revised (CUDIT-R)

Have you used any cannabis over the past six months? **YES / NO**

If YES, please answer the following questions about your cannabis use. Circle the response that is most correct for you in relation to your cannabis use *over the past six months*

1. How often do you use cannabis?

Never	Monthly or less	2-4 times a month	2-3 times a week	4 or more times a week
0	1	2	3	4

2. How many hours were you "stoned" on a typical day when you had been using cannabis?

Less than 1	1 or 2	3 or 4	5 or 6	7 or more
0	1	2	3	4

3. How often during the past 6 months did you find that you were not able to stop using cannabis once you had started?

Never	Less than monthly	Monthly	Weekly	Daily or almost daily
0	1	2	3	4

4. How often during the past 6 months did you fail to do what was normally expected from you because of using cannabis?

Never	Less than monthly	Monthly	Weekly	Daily or almost daily
0	1	2	3	4

5. How often in the past 6 months have you devoted a great deal of your time to getting, using, or recovering from cannabis?

Never	Less than monthly	Monthly	Weekly	Daily or almost daily
0	1	2	3	4

6. How often in the past 6 months have you had a problem with your memory or concentration after using cannabis?

Never	Less than monthly	Monthly	Weekly	Daily or almost daily
0	1	2	3	4

7. How often do you use cannabis in situations that could be physically hazardous, such as driving, operating machinery, or caring for children:

Never	Less than monthly	Monthly	Weekly	Daily or almost daily
0	1	2	3	4

8. Have you ever thought about cutting down, or stopping, your use of cannabis?

Never	Yes, but not in the past 6 months	Yes, during the past 6 months
0	2	4

This scale is in the public domain and is free to use with appropriate citation:

Adamson SJ, Kay-Lambkin FJ, Baker AL, Lewin TJ, Thornton L, Kelly BJ, and Sellman JD. (2010). An Improved Brief Measure of Cannabis Misuse: The Cannabis Use Disorders Identification Test – Revised (CUDIT-R). *Drug and Alcohol Dependence* 110:137-143.

CAGE-AID

CAGE-AID Questionnaire

Patient Name _____ Date of Visit _____

When thinking about drug use, include illegal drug use and the use of prescription drug use other than prescribed.

Questions:	YES	NO
1. Have you ever felt that you ought to cut down on your drinking or drug use?	☐	☐
2. Have people annoyed you by criticizing your drinking or drug use?	☐	☐
3. Have you ever felt bad or guilty about your drinking or drug use?	☐	☐
4. Have you ever had a drink or used drugs first thing in the morning to steady your nerves or to get rid of a hangover?	☐	☐



Opioid Risk Tool (ORT)

Opioid Risk Tool

This tool should be administered to patients upon an initial visit prior to beginning opioid therapy for pain management. A score of 3 or lower indicates low risk for future opioid abuse, a score of 4 to 7 indicates moderate risk for opioid abuse, and a score of 8 or higher indicates a high risk for opioid abuse.

Mark each box that applies	Female	Male
Family history of substance abuse		
Alcohol	1	3
Illegal drugs	2	3
Rx drugs	4	4
Personal history of substance abuse		
Alcohol	3	3
Illegal drugs	4	4
Rx drugs	5	5
Age between 16—45 years	1	1
History of preadolescent sexual abuse	3	0
Psychological disease		
ADD, OCD, bipolar, schizophrenia	2	2
Depression	1	1
Scoring totals		

CAGE-AID JA Ewing. Detecting Alcoholism. The CAGE Questionnaire. 252(14): *JAMA* 1905-7. 1984.

Webster LR, Webster R. Predicting aberrant behaviors in Opioid-treated patients: preliminary validation of the Opioid risk tool. *Pain Med.* 2005;6(6):432

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Overdose

- Cannabis or THC overdose can produce dose-dependent 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
- Oral ingestion of cannabis may increase the risk of overdose due to its delayed onset of effect. If overdose is due to ingestion then activated charcoal may be administered
- 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
RxTx Ottawa (ON): Canadian Pharmacists Association; c2018. CPS online: Cannabis

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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 PGP
- 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

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

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- University of Waterloo. Cannabis 101 {Infographic} https://uwaterloo.ca/pharmacy/sites/ca.pharmacy/files/uploads/files/cannabis_infographic_bw.pdf

Please proceed to the next module:

The Pharmacist's Role: Professional and Ethical Responsibilities Towards All Patients Using Cannabis