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Medical Cannabis Program

Cannabis N*ugs*O*f*W*isdom*

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Disclaimer

- The opinions shared during this meeting do not necessarily reflect the position of the Medical Cannabis Program.
- The Medical Cannabis Program does not endorse any specific product, producer, or vendor.

Lower-Risk Cannabis Use Guidelines (LRCUG)[1]

- Initially developed in 2017 as an evidence-based population health and prevention tool.
- Goal is to reduce modifiable risk factors of cannabis–related adverse health outcomes.
- Scientific evidence has evolved so new up-to-date guidelines based on this evidence were needed.
  - International Journal of Drug Policy – Jan. 2022

Method

- Targeted literature searches conducted
- Topical areas were informed by previous LRCUG

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Results

- Twelve recommendation clusters
- Three precautionary statements

Apply to both non-medical and medical use

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Recommendation #1[1]

- The initiation of cannabis use should be delayed until after late adolescence, or the completion of puberty, to reduce development-related vulnerabilities for harm.

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Why?[1]

- **Young** PWUC may be **more vulnerable** to adverse effects from cannabis use because of ongoing neurological, mental, and psycho-social development.
- **Early initiation** of cannabis use (i.e., that beginning before late adolescence or the completion of puberty) is associated with **adverse health and psycho-social effects**, especially in those who engage in intensive use (e.g., high-frequency use of potent cannabis products) and have other vulnerabilities.

Deeper Dive

Age of use onset

- Systematic and other reviews of human neuroimaging studies suggest that adolescent cannabis use is associated with structural brain alterations expressed in reduced volumes in the hippocampus and orbitofrontal cortex, thicker cerebral cortices, and decreased integrity of prefrontal and medial temporal brain regions.[2]
- Earlier age-of-initiation was associated with a higher risk for psychosis in all but one study and with increased symptoms of depression or anxiety by age 25.[3]

Recommendation #2[1]

- PWUC should use ‘low-potency’ cannabis products, (i.e., cannabis products with ideally lower total THC content, or a high CBD/THC content ratio).

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Why?[1]

- The higher the total or relative THC-content of cannabis that is used, the greater the risks of acute and chronic adverse mental or physical health outcomes.
- While CBD attenuates some of THC's adverse effects on mental and cognitive-behavioral outcomes and use of cannabis with high CBD content should be preferred, CBD use does not attenuate all of THC's adverse outcomes.

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Deeper Dive

Potency and composition

- High-potency cannabis use is associated with significantly higher anxiety and/or depression outcomes in youth.[4]
- Adolescents using high potency cannabis are less likely than older individuals to titrate their cannabis dose.[4]
- A systematic review found that CBD attenuates some of THC's acute psychoactive effects. However, it does not consistently improve memory and cognitive functions or reduce the level of intoxication produced by THC.[5]

Recommendation #3[1]

- All main available modes-of-use options come with some risk for harm; PWUC should refrain from cannabis ‘smoking’ and employ alternative routes-of-use for pulmonary health protection.

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Why?[1]

- Cannabis smoking can **harm the respiratory system**; this is particularly the case when tobacco is added.

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Deeper Dive

Modes of use

- A meta-analysis demonstrated that smoking cannabis alone was associated with significantly increased risk of cough, sputum production, wheezing, and dyspnea.[6]
- Chronic cannabis smoking (*without tobacco co-use*) increases the risk of chronic bronchitis, airway inflammation, bullous lung disease and pneumothorax, but it remains uncertain if it increases the risk of chronic obstructive pulmonary disease or lung cancer.[7]

Recommendation #4[1]

- If use occurs by inhalation, PWUC should avoid "deep inhalation", prolonged breath-holding, or similar inhalation practices.

Why?[1]

- These practices may be used by some PWUC with the aim of increasing absorption of THC and related psychoactive effects. However, they also **increase the intake of toxic content material** and the risk of **harm to the pulmonary system**.

Deeper Dive

Modes of use

- Cannabis continues to be commonly smoked in combination with tobacco in many settings, which makes it difficult to assess the respiratory health effects of cannabis smoking alone. Co-use of cannabis and tobacco does, however, increase risks of adverse respiratory health outcomes that may be exacerbated by intensive inhalation (e.g., 'deep inhalation' or breath holding) practices.[8]

Recommendation #5

- PWUC should refrain from frequent (e.g., daily or near-daily) or intensive (e.g., binging) cannabis use, and instead limit themselves to less frequent or occasional use.

Why?[1]

- Frequent or **intensive use patterns** are strongly associated with a multiplicity of severe **adverse outcomes** in mental and physical health (e.g., including neuro-cognitive deficits and dependence) and psycho-social domains.
- This is **especially** the case for intensive use beginning **at a young age** and sustained ('chronic') use over long periods of time.

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Deeper Dive

Frequency of use

- A systematic review including multiple meta-analyses of the associations between cannabis use and brain volume found that frequent cannabis use was associated with significantly smaller volumes in the hippocampus (involved in motivation, learning, memory), orbitofrontal cortex (involved in emotion and memory) and lateral regions than in controls.[9]

Recommendation #6[1]

- Where circumstances allow, PWUC should use legal and quality-controlled cannabis products and use devices.

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Why?[1]

- **Illegal cannabis products** are not regulated for quality and safety, and are typically not labelled for their THC and other content, and so may **increase risks of adverse experiences** and health problems.
- **Legally regulated cannabis products** are more **predictable** in their composition and potency, especially when there is product content **labelling**, and presumably safer because of their regulated production and other quality standards that **minimize the contaminants** that they may contain.

Deeper Dive

Potency and composition

- A systematic review also suggests that many, especially un-regulated cannabis products contain toxic contaminants such as microbes (e.g., molds), heavy metals, pesticides, and residual solvents. Their direct human impact may increase the risks of infections, carcinogenicity, and adverse reproductive effects, with the magnitude and route of exposure likely to influence outcomes.[10]

Recommendation #7[1]

- PWUC who experience impaired cognitive performance should consider temporarily suspending or substantially reducing the intensity (e.g., frequency/potency) of their cannabis use.

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Why?[1]

- Intensive cannabis use can impair neurocognitive function and produce other adverse health outcomes with ongoing use.
- There is some evidence that these adverse effects may at least partially reverse after relatively short periods (e.g., several days to weeks) of abstinence or very substantial reductions in the intensity of cannabis use.

Deeper Dive

Tolerance and effect reversal

- A double-blind, randomized, placebo-controlled study of the acute effects of cannabis use on neuro-behavioral functioning found that in subjects with occasional use, cannabis-induced alterations in brain functioning were associated with increased subjective intoxication and decreased behavioral performance.[11]
- Some adverse neuro-cognitive effects of cannabis on memory, learning and mental state may reverse after a period of abstinence or substantial reductions in use.[12]

Recommendation #8[1]

- PWUC should avoid driving a motor vehicle or operating machinery while under the influence of cannabis because of acute impairment and elevated risk of crash involvement, including injury or death.

Why?[1]

- Operating a motor-vehicle or other machinery while under the influence of cannabis and related impairment approximately **doubles the risk of MVC-involvement** that may result in injury or death.
- The **extent and duration of impairment and risk** for harm substantially **depends on** the **type** and **mode** of cannabis consumption, and the **user-individual's characteristics.**
- In general, the **more cannabis** is used and the **greater its potency** (THC), the **more severe the impairment**
- **Co-use of alcohol** with cannabis furthermore **increases multifold** driving impairment and should be avoided

Deeper Dive

Driving

- While cannabis-using individuals appear to compensate for some cannabis-related impairing effects at low doses, impairment is estimated to begin at around 5ng/ml THC-blood concentration and to increase with the amount and potency of the cannabis consumed, although probably not linearly[13]
- Importantly, THC-related impairments may persist for several hours after acute intoxication, depending on the specific characteristics of use and the user-individual[14]
- Using cannabis together with alcohol increases multifold the impairment of driving-relevant performance skills and MVC involvement risk (e.g., 5- to 10-fold)[15]

Recommendation #9[1]

- It is prudent for people who intend to procreate and for women who are pregnant or breastfeeding to abstain from cannabis use towards reducing possible risks for reproduction and of health harm to offspring, respectively.

Why?[1]

- There is some evidence that especially intensive cannabis use may somewhat **compromise reproductive abilities for women and men**.
- Cannabis use, especially during pregnancy, may **adversely affect** some pre- and post-natal health outcomes in **offspring**.
- Cannabinoids may also be passed on to infants via **breastmilk**.

Deeper Dive

Reproduction, pregnancy, & breastfeeding

- Males with chronic, intensive cannabis use had significantly lower sperm counts than those who used less often, suggesting dose-dependent effects.[16]
- Cannabis use also negatively affects sperm morphology, motility, viability, and fertilization capacity.[16]
- A systematic review and meta-analysis found men reporting cannabis use were twice as likely as controls to report erectile dysfunction.[17]
- Cannabis exposure reduces female fertility by reducing estrogen and progesterone levels, producing anovulatory menstrual cycles, and increasing the follicular phase length of reproductive cycles.[18]

Deeper Dive

Reproduction, pregnancy, & breastfeeding

- Breastfed infants were estimated to have ingested 2.5% of the maternal THC dose.[19]
- An analysis of human milk samples from cannabis-using breastfeeding women found measurable levels of THC in a majority and CBD in about 10% of the samples.[20]

Recommendation #10[1]

- PWUC should exercise general caution in combining other psychoactive substances with cannabis use.

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Why?[1]

- The concurrent use of cannabis and other psychoactive substances or psychotropic medications can **amplify the risks** of some harms to health. For example, the frequent use of cannabis and tobacco and/or alcohol can magnify risks for a variety of adverse outcomes (e.g., dependence, pulmonary or reproductive health, besides acute impairment from alcohol).
- Cannabinoids can also **influence metabolic processes** in ways that adversely interact with a variety of medications (e.g., protease inhibitors, psychotropics).

Deeper Dive

Interactions with other psychoactive substances

- Adolescents who co-use *tobacco and cannabis* report more problems with and dependence on both drugs, consume more alcohol, and experience stronger withdrawal symptoms than those individuals with singular drug use.[21]
- Comprehensive reviews suggest that frequent *cannabis and alcohol* co-use by adolescents is associated with greater neuropsychological impairments, adverse health and psycho-social outcomes, such as poorer academic performance and impaired driving.[22]

Deeper Dive

Interactions with other psychoactive substances

- Interactions between *cannabis* and other psychotropic drugs, for example, *psychostimulants*, may negatively influence physical and mental health outcomes.[23]
- Cannabinoids can inhibit the liver and other enzymatic systems, increasing the plasma levels and hence the toxicity of other psychotropic drugs via adverse *drug-drug interactions*.[24]
- They both can interact *with tricyclic antidepressants, central nervous system depressants, protease inhibitors, and warfarin therapy*.[25]

Clinically Relevant Interactions[26]

Clinical Relevance of Drug interactions with Cannabis		
Drug	**Mechanism**	**Effects**
Level 1 Interaction: Very High Risk		
Warfarin	CYP2C9 Inhibition	Increased INR with concomitant use of CBD resulting in GI bleeding. Monitor INR closely for warfarin adjustments. Avoid combination if possible.
Level 2 Interaction: High Risk		
Buprenorphine	CYP3A4 Inhibition	Increased concentrations of buprenorphine. Avoid combination if possible or adjust buprenorphine doses.[1]
Tacrolimus	CYP3A4 Inhibition	Increased tacrolimus concentrations. Avoid combination if possible or adjust tacrolimus doses.[1]
Level 3 Interaction: Medium Risk		
Clozapine	CYP3A4 and 2C19 Induction	Decreased clozapine concentrations. Consider dose adjustment.[1]
Methadone	CYP3A4 and 2C19 Inhibition	Increased methadone levels resulting in increased somnolence. Consider dose adjustment.[1]
Clobazam	CYP2C19 Inhibition	Increased clobazam concentrations. Consider dose adjustment.[1]
Chlorpromazine	Possible CYP1A2 Induction	Decreased chlorpromazine concentrations. Consider dose adjustment.[1]
Hexobarbital	Possible CYP3A4 Inhibition	Increased hexobarbital concentrations. Consider dose adjustment.[1]
Ketoconazole	CYP3A4 Inhibition	Increased concentrations of THC/CBD
Rifampicin	CYP3A4 Induction	Decreased concentrations of THC/CBD
Stiripentol	CYP2C19 Induction	Increased concentrations of stiripentol. Consider dose adjustment.[1]
Theophylline	CYP1A2 Induction	Decreased theophylline concentration. Consider dose adjustment.[1]
Valproate	Possible UGT1A9 and UGTB7 Inhibition	Increased LFTs. Assess liver function before taking in combination.
Level 5 Interaction: Co-administration with CBD does not lead to significant changes in drug levels (rufinamide, topiramate, zonisamide, nelfinavir)		

Levels of clinical relevance of drug interactions were determined according to the combination of severity and probability of occurrence.
[1]Monitor plasma levels if possible.

Recommendation #11[1]

- Some specific groups of people are at elevated risk for cannabis use-related health problems because of biological pre-dispositions or co-morbidities. They should accordingly avoid or adjust their cannabis use.

Why?[1]

- Higher risks for harm extend to individuals with a genetic predisposition.
- Individuals with preexisting cardio-vascular risks may be at increased risk of acute harm especially if they inhale high-potency products.
- Female PWUC may be at risk of developing cannabis use-related problems more quickly or more severely than men.
- Older-age PWUC may be at increased risk for some adverse outcomes because of general ageing-related deficits, other co-morbid chronic diseases, and/or the use of other psychotropic drugs.

Deeper Dive

Special risk factors/groups

- It appears that THC exposure can exert substantial stress on the cardiovascular system, especially in individuals with novice or occasional use and consequentially limited tolerance to its effects.[27]
- In those affected by mental health problems (e.g., psychosis or depression) the prevalence of cannabis use is commonly elevated and associated with increased disease severity, progression or outcome severity.[28]

Deeper Dive

Special risk factors/groups

- Male PWUC develop CUD more often and typically express more problem symptoms than females.[29]
- Females exhibited greater peak-THC concentrations in blood and subjective effects as well as ratings of “anxious/nervous,” “heart racing,” and “restless” than males, suggesting differential effect profiles.[29]
- For older-age PWUC, cannabis-related impairment of cognitive and executive functions and reaction/memory may amplify age-related declines in these abilities.[30]

Recommendation #12[1]

- The combination of risk-factors for adverse health outcomes from cannabis use further amplifies the likelihood of experiencing severe harms and should be avoided.

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Why?[1]

- Research on the combinations of cannabis-related risk behaviors is limited but it is plausible that the more risk factors one has the greater the risk and severity of adverse outcomes from using cannabis.
- Overall, the strongest evidence suggests that combining frequent, intensive use of high-potency cannabis products, especially at a young age (e.g., adolescence), substantially increases the risk of key acute or chronic adverse outcomes and harms (e.g., mental health, neuro-cognition, dependence).

Deeper Dive

Combination of risks

- Individuals with combinations of the risk factors identified above are likely to be at markedly elevated risk of experiencing cannabis-related adverse health outcomes.[31]
- The combination of greatest concern is the high-frequency use of high-potency cannabis products, especially when initiated at and sustained from a young age. This pattern predicts increased risks of multiple adverse mental and physical outcomes, including neuro-cognitive, psychosis and cardio-vascular problems.[32]

General Precaution A

- People who use cannabis (PWUC) need to know that there is no universally safe level of cannabis use; thus, the only reliable way to avoid any risk for harm from using cannabis is to abstain from its use.

General Precaution B

- Frequent cannabis use, and especially intensive use over longer periods, can lead to a ‘cannabis use disorder’ (CUD) or cannabis dependence, that may require treatment.

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General Precaution C

- PWUC should exercise social consideration and responsibility in avoiding cannabis use that may result in harm-to-others.

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Any questions?

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