

Vital Link



The Journal of the Canadian Association of Naturopathic Doctors

Addressing Risk Factors for Chronic Disease

Volume 26, Issue 4

Adult-use Cannabis: What a Naturopathic Doctor Should Know

Dr. Paola Cubillos, M.D, N.D, Medical Director – Colombia, CB2 Insights

Editor's Note: This article pertains to the use of recreational Cannabis. NDs in Canada are reminded that they must follow the policies/guidelines established by their regulator when engaging with patients about recreational Cannabis and that NDs in Canada do not currently have the legal authority to authorize Cannabis for medical use.

Adult-use Cannabis: What a Naturopathic Doctor Should Know

Dr. Paola Cubillos, M.D, N.D, Medical Director – Colombia, CB2 Insights



Canada took a bold step with the legalization of the most widely used illicit substance on the planet: cannabis.¹ The intent of the Canadian government enacting the adult-use regulation is to “keep cannabis out of the hands of youth; keep profits out of the pockets of criminals; protect public health and safety by allowing adults access to legal cannabis”.²

As of October 17, 2018, Canadians who are 18 years or older (note: age varies by province) are allowed to possess up to 30 grams of dried (or equivalent in non-dried form) cannabis which has been sourced from a legal supplier. Adults are also permitted to share up to 30 grams of legal cannabis with other adults, buy dried and fresh cannabis from a licensed retailer or online from a federally-licensed producer, and grow up to four cannabis plants per residence, from a licensed seed or seedling supplier.²

While expanded availability of products under the legal framework was expected to result in increased consumption, recent Health Canada reports show that only 5% more Canadians consumed cannabis in the second quarter of 2019 compared to the second quarter of 2018.⁵ Even pre-legalization, Canada has displayed some of the highest rates of cannabis consumption,⁴ lower than the USA, which has an annual prevalence of cannabis use of 18.4% but higher than most European countries (reference https://dataunodc.un.org/drugs/prevalence_map_2017)

Now, in what has been dubbed by the media as “Cannabis 2.0”, the Federal government has established regulations for the production and sale of edible cannabis, cannabis extracts and topical cannabis. These products are expected to be available for Canadians to purchase in early 2020.³

The rapidly changing adult-use cannabis landscape in Canada poses challenges for NDs, as healthcare professionals who focus on health promotion and prevention. While cannabis has been used by humans for thousands of years, given its illegal status worldwide for most of the last century, to date there has been little standardized research to guide NDs to fully understand its impact on human health, both short and long term. That being said, even with current scope

prohibitions on authorizing medicinal cannabis, NDs still need to be able to discuss basic aspects of recreational cannabis harm reduction from an evidence-based viewpoint. The intent of this article is to elaborate on the more salient aspects of cannabis effects on human health and harm reduction strategies naturopathic doctors should know as Canada undertakes one of the most important public health experiments in modern history.⁶

Cannabis Use by Canadians

Prior to 2018, national survey data demonstrated high cannabis consumption levels in Canada, with use rising 4-5 years before adult-use legalization, reported across all age groups.⁷ Since early 2018, Statistics Canada has also been collecting self-reported consumption and purchasing data, publishing their findings quarterly under the title *National Cannabis Survey*. According to their data, the prevalence of cannabis consumption has remained somewhat unchanged since the legislation came into effect; the second quarter of 2019, for example, reported consumption returned to pre-legalization levels after a slight increase in the first quarter. Males were also twice as likely as females to have used cannabis, were more likely to use cannabis daily or almost daily, and are more likely to use cannabis for non-medical reasons. This report also revealed that about 4.9 million Canadians, or 16% of Canadians aged 15 or older, reported using cannabis post-legalization;⁸ the first quarter of 2019, recorded an increase in first-time users, to 646,000 from 327,000 in the first quarter of 2018; however, somewhat surprisingly, over half of these new users were aged 45 and older. Consumption patterns among young people, ages 15-25 remains unchanged, at around 30%.⁹ Although this trend has not varied from before legalization, 6.1% of Canadians aged 15 and older (1.8 million) reported using cannabis on a daily or almost daily basis.¹⁰

Cannabis administration routes

According to the National Cannabis Survey, smoking remains the most common method of consuming cannabis, with approximately two-thirds of male (68%) and female (62%) consumers choosing this method in 2019. Smoking exposes the dried cannabis flower to very high temperatures, which allows for the decarboxylation of the different cannabinoids.¹¹ Cannabinoids are a group of C21 compounds occurring in resin produced by glandular hairs of *C. sativa* L. Among the over 420 known constituents of cannabis, more than 60 belong to cannabinoids, which chemically belong to the terpenophenol group of compounds.¹² In their decarboxylated forms, cannabinoids — such as delta-9-tetrahydrocannabinol (THC) and

cannabidiol (CBD), are readily absorbed in the bloodstream via the lungs, and reach different systems to exert their effects through the interaction with endocannabinoid receptors: CB1, which is mainly present in the central nervous system, and CB2, localized in the spleen and other organs associated with immune function.¹³ While the two major cannabinoids can be considered “psychoactive” (both impacting brain function) THC is the component more commonly associated with the intoxicating effects of cannabis, while CBD is thought to ‘counteract’ the effects of THC.¹⁴

Intrapulmonary administration of cannabinoids by smoking is considered to be an effective delivery method due to the high systemic bioavailability, fast onset of action, short duration of peak effects and limited duration of effects as compared to other administration methods such as ingestion.¹⁵ Vaporization of dry flower or cannabis extracts relies on lower temperatures, while achieving similar results.

Cannabis oils are increasing in popularity, particularly with older adults who are experimenting with cannabis for the first time. These oils are meant to be ingested therefore their pharmacokinetics are influenced by first-pass metabolism. Oral THC bioavailability has been reported to be 10-20%,¹⁶ demonstrating peak plasma concentrations at 4-6 hours after ingestion. Hepatic metabolism of delta-9-THC results in the production of higher amounts of 11-OH-THC, a highly active metabolic compound which has been suggested to have increased psychoactive properties when compared to delta-9-THC.^{17, 18, 11}

Oral preparations, commonly known as ‘edibles’ are an increasing cannabis market segment and products that Canadians will soon be able to legally purchase for recreational use. Under the amendments to the official Cannabis Regulations, which came into effect on October 17, 2019, Health Canada has stipulated a series of requirements that edibles, cannabis extracts and cannabis topicals should meet in order to be allowed for sale.¹⁹ Edible cannabis, either for eating or drinking, can have up to 10 mg of THC per package, and cannabis extracts meant for ingestion can contain up to 10 mg per unit. Other packaging and labeling restrictions are placed on these products to minimize the appeal to children and youth.^{3, 19} Consumption of oral preparations follow similar pharmacokinetics and pharmacodynamics as cannabis oils, are subjected to first pass metabolism described above, and demonstrates distinct pharmacokinetics patterns when compared to the inhalation routes of administration. Onset of “drug” effects are generally perceived 30-60 minutes after ingestion, with a sustained peak effect that occurs 90 to 180 minutes after exposure, and a gradual return to baseline 6-8 hours post-administration.²⁰ Given that onset of symptoms when using cannabis edibles is delayed, over intoxication is more likely to occur with these products. It is recommended therefore that adult users begin with a smaller dose of THC than that permitted by the regulations, particularly for those who are not experienced cannabis users.²¹

While the Canadian regulations specifically stipulate that edibles packaging must be plain, child resistant, and not include elements

that may appeal to youth or children, one of the risks associated with these kinds of products is unintentional consumption by children or pets. A review of data from the US National Poison Data System from 2005 to 2011 found that decriminalization of cannabis was associated with increased reports of unintentional exposures in young children up to 9 years of age.²² A more recent review of National Poison Data System data showed similar increases in edibles-related calls to poison control centers from 2013 to 2015.²³ In Canada, 16 cases of children that have suffered serious adverse events involving cannabis in the months around legalization have been reported, according to preliminary data from the Canadian Pediatric Surveillance Program study.²⁴

Short term cannabis effects

Individual susceptibilities and previous cannabis experience influence the effects exerted by cannabis, particularly THC. Acute effects of cannabis use include euphoria, impaired short-term memory, impaired motor coordination which interferes with driving skills, inattentiveness, altered judgement, increased anxiety, challenges in processing and retaining information, and paranoia in extreme cases.²⁵ On a physiological level, cannabis use may lead to dry mouth, conjunctival injection, tachycardia and hypotension.²⁶ Hemodynamic changes are implicated as the cause of the different adverse cardiovascular events that have been seen acutely with cannabis use (particularly high THC products) such as arrhythmias and acute myocardial infarction, both in young and adult users with comorbidities.^{27, 28, 29}

Long term effects of cannabis use

Long term cognitive effects and challenges for regular cannabis users are of particular importance for adolescents, as early and/or frequent cannabis use is associated with poor long-term outcomes.³⁰ Limited evidence suggests that frequent cannabis use during adolescence is related to impairments in subsequent academic achievement and education, employment and income, and social relationships and social roles.³¹ While the different methodologies employed to assess the long-term cognitive impact of cannabis, the various types of cognitive measures researched, and variability in length and frequency and exposure studied may lead to discrepancies across the studies that have shed light on the impact of cannabis use, generally speaking, studies agree that chronic cannabis users are at higher risk of suffering various degrees of cognitive impairment that can potentially be long-lasting particularly if use starts early during adolescence, is frequent and persists for years.^{32, 33}

The risk of cannabis dependence (defined as lack of control over use despite associated harms) is considered to be approximately 9% among individuals with any lifetime cannabis use.³⁴ The rate increases to approximately 16% for those who initiate cannabis use during adolescence.³⁵ Additionally, while most cannabis users do not develop dependence, heavy cannabis use in adolescence is also linked to increased dependence risk.³⁶

Connection with mental illness

Although the relationship between cannabis use and mental health issues is complex and generally poorly understood, numerous studies have established a connection between cannabis use and psychotic syndromes and/or schizophrenia. In *The Health effects of Cannabis and Cannabinoids* report by the National Academies of Science, Engineering and Medicines in the US, the authors determined there is substantial evidence of a statistical association between cannabis use and the development of schizophrenia or other psychoses, with most frequent users being at highest risk.³¹ To date, establishing causality between cannabis use and the development of mental health disorders has been difficult. Both epidemiological and experimental studies consistently suggest a link between heavy cannabis use and risk of psychosis, however one statistic that speaks against this association is the fact that while cannabis use has increased in some populations, the incidence of psychosis has not.³⁷

There are consumption patterns that have been associated with higher risk for the development of psychotic illness or schizophrenia, such as earlier onset cannabis use, particularly for those under age 16,^{38, 39} and higher frequency use and higher potency products.^{40, 41} Considering genetic predispositions is also relevant when discussing cannabis use and mental health issues, as studies have demonstrated that schizophrenia symptoms can be precipitated by cannabis use in those with genetic predispositions,⁴² and those cannabis users with a family history of psychosis can be 2.5 to 10 times more likely to develop psychotic disorders compared to non-users with a family history.⁴³ The relationship between cannabis use and schizophrenia becomes even more complex when the possibility that cannabis use may represent self-medication of early schizophrenia symptom management is considered.^{44, 45}

Risks from cannabis use vs. other substances

Cannabis is not a harmless substance, despite the shifting perceptions harbored by the general public, young people in particular.⁴⁶ It is useful, however, to contrast the harm associated with cannabis use, both on a societal and individual level, with other legal and illegal recreational substances. Nutt *et al* assessed the harm caused by a variety of substances based on 16 different criteria and reached the conclusion that the most harmful drugs to drug users were heroin, crack cocaine and methamphetamine, while the most harmful to others were alcohol, followed by heroin and crack cocaine. In their scoring system, alcohol was assigned a score of 72 (cumulative for the sum of the weights of all criteria of harm to users and harm to others), cocaine a score of 27, tobacco 26 and cannabis 20.⁴⁷ Results from similar analysis undertaken by Lachenmeier and Rehm conclude that “the risk of cannabis may have been overestimated in the past. At least for the endpoint of mortality, the margin of exposure for THC/Cannabis in both individual and population-based assessments would be above safety thresholds. In contrast, the risk of alcohol, may have been commonly underestimated”.⁴⁸

Medication Interactions

Regular cannabis use is thought to cause induction of the CYP1A2 enzyme, which may decrease concentrations of 1A2 substrates,⁴⁹ including aminophylline, caffeine, clozapine, duloxetine, estradiol, estrogens, lidocaine, melatonin, olanzapine, and zolmitriptan. The CYP3A4 pathway is also involved in the metabolism of the major cannabinoids THC and CBD. 3A4 inhibitors have been shown to increase serum concentrations of these cannabinoids, while inducers have the opposite effect.⁵⁰ Cannabis can also increase the sedative, psychomotor, respirator and other effects of CNS depressant drugs and alcohol.^{51, 52} CBD use may increase serum concentrations of macrolides, calcium channel blockers, benzodiazepines, cyclosporine, sildenafil, antihistamines, haloperidol, antiretrovirals, and some statins, due to its action on CYP3A4.⁵³ It may also increase serum concentrations of SSRIs, tricyclic antidepressants, antipsychotics, beta blockers and opioids (including codeine and oxycodone), as it exerts an effect on CYP2D6.⁵⁴

Cannabis effect on driving

Experimental studies suggest that THC predominant cannabis leads to the impairment of cognitive and psychomotor skills required for safe driving.⁵⁵ Psychomotor testing performance has been found to decrease for up to five to six hours after smoking cannabis, with the majority of impairment occurring in the first two hours after smoking, although others suggest a window of at least three to six hours after smoking.⁵⁶ Meta-analyses have concluded that cannabis use increases the risk of being involved in a motor-vehicle accident, and such risk has been found to be double or more than double in some studies.^{57, 58}

Harm reduction strategies

Both federal and provincial agencies in Canada have assessed the evidence to formulate cannabis harm risk reduction strategies. These strategies commonly tackle the issues highlighted in this article, and particularly emphasize the need to prevent early adolescent use.^{59, 60} For instance, Canada’s *Low Risk Cannabis Use* Guidelines, created by the Canadian Research Initiative on Substance Misuse and the Centre for Addiction and Mental Health provides a set of evidence-based guidelines around abstinence, early initiation of cannabis use, THC content, combusted administration, inhalation practices, frequency and intensity of use, driving, and at-risk populations.³⁸

These lower-risk use guidelines (LRUG) include: Abstinence as the best way to avoid cannabis associated risks, delaying taking up cannabis use until later in life, identify and choose lower-risk cannabis products — generally considered to be those with a lower percentage content of THC and a higher percent content of CBD, avoid use of synthetic cannabis products, avoid smoking burnt cannabis, avoiding harmful smoking practices such as deep inhalations or breath-holding, limit and reduce frequency of use, avoid driving or operating machinery for at least 6 hours after using cannabis, avoid combining with alcohol as it can increase impairment, avoid using cannabis if the person is at risk of mental health issues or if they are pregnant, and avoid combining any of the risk factors related to cannabis use.⁶¹

Currently naturopathic doctors in Canada are not permitted to recommend cannabis- based products to their patients or authorize cannabis for medical use. In BC, NDs with prescribing authority are permitted to prescribe a drug containing cannabis in accordance with the Cannabis Act and regulations. The Standards, Limits and Conditions for Prescribing, Dispensing and Compounding Drugs sets out what is permitted with respect to drugs in BC.⁶² Ontario does not include Cannabis in the Prescription Drug List and NAPRA Schedule 1 that Members who have met the standard of practice for prescribing with CONO may prescribe.⁶³ Nonetheless, as primary care providers, NDs are strongly encouraged to review these resources and to become comfortable discussing the different evidence-based harm-reduction strategies available in order to properly counsel their patients on how to minimize the impact of cannabis use. In its Practice Guideline: *Non-medical (Recreational) Cannabis*, the College of Naturopaths of Ontario (CONO) states that “Members who possess the knowledge, skill and judgment specific to cannabis may where appropriate provide guidance to patients who are interested in incorporating non-medical (recreational) cannabis into their lives”.⁶⁴

As cannabis use becomes more prevalent and more accepted in our society, naturopathic doctors should consider routinely screening for cannabis use, particularly groups in which higher use is expected, such as youth and chronic pain patients, and to counsel individuals on how to minimize risk. Naturopathic doctors should also enquire about cannabis use in patients with conditions known to be exacerbated by cannabis use, such as insomnia, mood and psychotic disorders, chronic cough, and for those with impaired performance at school or work.

Additionally, NDs should also learn to distinguish between low-risk and problematic use, based on quantity and frequency of use. Indicators of problematic cannabis use may include daily use, reporting anxiety as primary reason to use cannabis, unsuccessful attempts to quit, and medical, social or financial issues arising from cannabis use.⁶⁵ If the suspicion of problematic cannabis use arises, NDs should consider using a validated screening questionnaire, such as CUDIT-R, and refer those patients with problematic use to specialized care, while ensuring that patients stay connected to their trusted primary care provider.

Vaping cannabis – an emerging issue

1479 cases of e-cigarette or vaping product use- associated lung injury (EVALI), and 33 deaths, have been reported in the United States in a span of 4 months in 2019. This illness, that is marked by chest pain, dyspnea and vomiting has affected mainly young people, and the majority of cases have been linked to *illegal* THC vaping cartridges.⁶⁶ While the exact cause of these illnesses is not known, it is believed that the lung damage is associated with the use of additives, preservatives and/or heavy metals present in the e-cigarette aerosols, such as vitamin E acetate.⁶⁷ No studies have been conducted to determine the short or long term effects of vaporized cannabis extracts (as opposed to the use of devices that rely on dry herb) and while these products were made legal as of October 2019,

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 0	Monthly or less 1	2-4 times a month 2	2-3 times a week 3	4 or more times a week 4
2. How many hours were you “stoned” on a typical day when you had been using cannabis?	Less than 1 0	1 or 2 1	3 or 4 2	5 or 6 3	7 or more 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 0	Less than monthly 1	Monthly 2	Weekly 3	Daily or almost daily 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 0	Less than monthly 1	Monthly 2	Weekly 3	Daily or almost daily 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 0	Less than monthly 1	Monthly 2	Weekly 3	Daily or almost daily 4
6. How often in the past 6 months have you had a problem with your memory or concentration after using cannabis?	Never 0	Less than monthly 1	Monthly 2	Weekly 3	Daily or almost daily 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 0	Less than monthly 1	Monthly 2	Weekly 3	Daily or almost daily 4
8. Have you ever thought about cutting down, or stopping, your use of cannabis?	Never 0	Yes, but not in the past 6 months 2	Yes, during the past 6 months 4		

Scores of 8 or more indicate hazardous cannabis use. Scores of 12 or more indicate a possible cannabis use disorder, for which further intervention may be required.

For further interpretation see: Adamson S, Kay-Lambkin F, Baker A, et al. An improved brief measure of cannabis misuse: The Cannabis Use Disorders Identification Test – Revised (CUDIT-R). *Drug Alcohol Depend* 2010; (In Press). www.bpac.org.nz keyword: addiction-tools

such products have yet to reach the licensed Canadian market. Since vaping cannabis has become very prevalent among adolescents,⁶⁸ it is important to discuss the unknown health effects of vaporizing cannabis oils with users, and emphasize the potential issues associated with illegal, unregulated market products.

Conclusions

Cannabis use is very common in Canada, chiefly among young Canadians. While its full effects on human health have not been entirely elucidated, there is a good amount of information on evidence-based strategies that can be undertaken by individuals interested in using cannabis to reduce risks and harms. Naturopathic doctors, as health care professionals well trained in engaging with their patients on issues related to disease prevention, are well positioned to counsel on these strategies and to recognize patterns of problematic use and refer to the proper specialties for treatment. With ‘Cannabis 2.0’, new ways for Canadians to use cannabis have been made legal, therefore health care providers should become aware of the impact the use of these products may have on people’s health. 🌿

About the Author

Dr. Paola Cubillos, MD, ND received her medical degree from the Universidad del Rosario in Colombia and her naturopathic medical degree from CCNM. Dr. Paola focuses on expanding the knowledge base on evidence-based applications for medical cannabis, spearheading medical cannabis research, participating in international collaborations and creating spaces for training health care professionals on medical cannabis. Dr. Cubillos has lectured on such topics as: common medical cannabis misconceptions; medical cannabis and PTSD and the use of medical cannabis in the treatment of pain. Dr. Paola is currently Medical Director – Colombia for CB2 Insights, a member of the CCNM Research Ethics Committee and Chair of the Research Ethics Board at Clinica Las Américas in Medellín, Columbia.

References

1. WHO | Cannabis. December 2010. https://www.who.int/substance_abuse/facts/cannabis/en/. Accessed December 10, 2019.
2. Government of Canada, Department of Justice, Electronic Communications. Cannabis Legalization and Regulation. <https://www.justice.gc.ca/eng/cj-jp/cannabis/>. Published June 20, 2018. Accessed October 20, 2019.
3. Health Canada. Proposed regulations for additional cannabis products - Canada. <https://www.canada.ca/en/health-canada/services/drugs-medication/cannabis/resources/regulations-edible-cannabis-extracts-topicals.html>. Published July 3, 2019. Accessed October 20, 2019.
4. WHO | The health and social effects of nonmedical cannabis use. March 2016. https://www.who.int/substance_abuse/publications/cannabis_report/en/index5.html. Accessed October 20, 2019.
5. Government of Canada, Statistics Canada. Add/Remove data - Prevalence of cannabis use in the past three months, self-reported. <https://www150.statcan.gc.ca/t1/tbl1/en/cv.action?pid=1310038301>. Published February 7, 2019. Accessed October 20, 2019.
6. Kelsall D. Watching Canada’s experiment with legal cannabis. *CMAJ*. 2018;190(41):E1218.
7. Macdonald R, Rotermann M. Analysis of trends in the prevalence of cannabis use in Canada, 1985 to 2015. Government of Canada, Statistics Canada. <https://www150.statcan.gc.ca/n1/pub/82-003-x/2018002/article/54908-eng.htm>. Published February 21, 2018. Accessed October 20, 2019.
8. Government of Canada, Statistics Canada. The Daily — National Cannabis Survey, second quarter 2019. <https://www150.statcan.gc.ca/n1/daily-quotidien/190815/dq190815a-eng.htm>. Published August 15, 2019. Accessed October 20, 2019.
9. Government of Canada, Statistics Canada. The Daily — National Cannabis Survey, first quarter 2019. <https://www150.statcan.gc.ca/n1/daily-quotidien/190502/dq190502a-eng.htm>. Published May 2, 2019. Accessed October 20, 2019.
10. Rotermann M. Analysis of trends in the prevalence of cannabis use and related metrics in Canada. *Health Rep*. 2019;30(6):3-13.
11. Sharma P, Murthy P, Bharath MMS. Chemistry, metabolism, and toxicology of cannabis: clinical implications. *Iran J Psychiatry*. 2012;7(4):149-156.
12. Psychoactive Drugs. In: *Pharmacognosy*. Academic Press; 2017:363-374.
13. Turcotte C, Blanchet M-R, Laviolette M, Flamand N. The CB2 receptor and its role as a regulator of inflammation. *Cell Mol Life Sci*. 2016;73(23):4449-4470.
14. Niesink RJM, van Laar MW. Does Cannabidiol Protect Against Adverse Psychological Effects of THC? *Front Psychiatry*. 2013;4:130.
15. Solowij N. Peering Through the Haze of Smoked vs Vaporized Cannabis-To Vape or Not to Vape? *JAMA Netw Open*. 2018;1(7):e184838.
16. Wall ME, Sadler BM, Brine D, Taylor H, Perez-Reyes M. Metabolism, disposition, and kinetics of delta-9-tetrahydrocannabinol in men and women. *Clin Pharmacol Ther*. 1983;34(3):352-363.
17. Lemberger L, Crabtree RE, Rowe HM. 11-hydroxy-9-tetrahydrocannabinol: pharmacology, disposition, and metabolism of a major metabolite of marijuana in man. *Science*. 1972;177(4043):62-64.
18. Lemberger L, Martz R, Rodda B, Forney R, Rowe H. Comparative pharmacology of Delta9-tetrahydrocannabinol and its metabolite, 11-OH-Delta9-tetrahydrocannabinol. *J Clin Invest*. 1973;52(10):2411-2417.
19. Health Canada. Health Canada finalizes regulations for the production and sale of edible cannabis, cannabis extracts and cannabis topicals - Canada.ca. Government of Canada News. <https://www.canada.ca/en/health-canada/news/2019/06/health-canada-finalizes-regulations-for-the-production-and-sale-of-edible-cannabis-cannabis-extracts-and-cannabis-topicals.html>. Published June 14, 2019. Accessed December 10, 2019.
20. Vandrey R, Herrmann ES, Mitchell JM, et al. Pharmacokinetic Profile of Oral Cannabis in Humans: Blood and Oral Fluid Disposition and Relation to Pharmacodynamic Outcomes. *J Anal Toxicol*. 2017;41(2):83-99.
21. Canadian Centre on Substance Use and Addiction : 7 Things You Need to Know about Edible Cannabis. <https://www.ccsa.ca/sites/default/files/2019-06/CCSA-7-Things-About-Edible-Cannabis-2019-en.pdf>. Accessed December 10, 2019.
22. Wang GS, Roosevelt G, Le Lait M-C, et al. Association of unintentional pediatric exposures with decriminalization of marijuana in the United States. *Ann Emerg Med*. 2014;63(6):684-689.

23. Cao D, Srisuma S, Bronstein AC, Hoyte CO. Characterization of edible marijuana product exposures reported to United States poison centers. *Clin Toxicol*. 2016;54(9):840-846.
24. Cannabis edibles already harming kids, new data show | CMAJ News. <https://cmajnews.com/2019/06/27/cannabis-edibles-already-harming-kids-new-data-show-cmaj-1095789/>. Accessed December 10, 2019.
25. Sumanasekera WK, Spio K. Cannabis (Marijuana): Psychoactive Properties, Addiction, Therapeutic Uses, and Toxicity. *Journal of Addictive Behaviors, Therapy & Rehabilitation*. 2018;2016. doi:10.4172/2324-9005.1000156
26. Spindle TR, Cone EJ, Schlienz NJ, et al. Acute Effects of Smoked and Vaporized Cannabis in Healthy Adults Who Infrequently Use Cannabis: A Crossover Trial. *JAMA Netw Open*. 2018;1(7):e184841.
27. Desai R, Fong HK, Shah K, et al. Rising Trends in Hospitalizations for Cardiovascular Events among Young Cannabis Users (18-39 Years) without Other Substance Abuse. *Medicina*. 2019;55(8). doi:10.3390/medicina55080438
28. Kariyanna P, Wengrofsky P, Jayarangaiah A, et al. Marijuana and Cardiac Arrhythmias: A Scoping Study. *International Journal of Clinical Research & Trials*. 2019;4(1). doi:10.15344/2456-8007/2019/132
29. Rajesh M, Mukhopadhyay P, Bhatkai S, et al. Cannabidiol attenuates cardiac dysfunction, oxidative stress, fibrosis, and inflammatory and cell death signaling pathways in diabetic cardiomyopathy. *J Am Coll Cardiol*. 2010;56(25):2115-2125.
30. Hasin DS. US Epidemiology of Cannabis Use and Associated Problems. *Neuropsychopharmacology*. 2018;43(1):195-212.
31. The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research : Health and Medicine Division. <http://nationalacademies.org/hmd/reports/2017/health-effects-of-cannabis-and-cannabinoids.aspx>. Accessed October 21, 2019.
32. Volkow ND, Baler RD, Compton WM, Weiss SRB. Adverse health effects of marijuana use. *N Engl J Med*. 2014;370(23):2219-2227.
33. Hall W. What has research over the past two decades revealed about the adverse health effects of recreational cannabis use? *Addiction*. 2015;110(1):19-35. doi:10.1111/add.12703
34. Lopez-Quintero C, Pérez de los Cobos J, Hasin DS, et al. Probability and predictors of transition from first use to dependence on nicotine, alcohol, cannabis, and cocaine: results of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). *Drug Alcohol Depend*. 2011;115(1-2):120-130.
35. Anthony JC, Alan Marlatt G. The Epidemiology of Cannabis Dependence. *Cannabis Dependence*:58-105. doi:10.1017/cbo9780511544248.006
36. Silins E, John Horwood L, Patton GC, et al. Young adult sequelae of adolescent cannabis use: an integrative analysis. *The Lancet Psychiatry*. 2014;1(4):286-293. doi:10.1016/s2215-0366(14)70307-4
37. Gage SH. Cannabis and psychosis: triangulating the evidence. *Lancet Psychiatry*. 2019;6(5):364-365.
38. Fischer B, Russell C, Sabioni P, et al. Lower-Risk Cannabis Use Guidelines: A Comprehensive Update of Evidence and Recommendations. *American Journal of Public Health*. 2017;107(8):1277-1277. doi:10.2105/ajph.2017.303818a
39. Marconi A, Di Forti M, Lewis CM, Murray RM, Vassos E. Meta-analysis of the Association Between the Level of Cannabis Use and Risk of Psychosis. *Schizophr Bull*. 2016;42(5):1262-1269.
40. Di Forti M, Sallis H, Allegrì F, et al. Daily use, especially of high-potency cannabis, drives the earlier onset of psychosis in cannabis users. *Schizophr Bull*. 2014;40(6):1509-1517.
41. Di Forti M, Quattrone D, Freeman TP, et al. The contribution of cannabis use to variation in the incidence of psychotic disorder across Europe (EU-GED): a multicentre case-control study. *Lancet Psychiatry*. 2019;6(5):427-436.
42. Pasmán JA, Verweij KJH, Gerring Z, et al. GWAS of lifetime cannabis use reveals new risk loci, genetic overlap with psychiatric traits, and a causal influence of schizophrenia. *Nat Neurosci*. 2018;21(9):1161-1170.
43. Radhakrishnan R, Wilkinson ST, D’Souza DC. Gone to pot—a review of the association between cannabis and psychosis. *Front Psychiatry*. 2014;5:54.
44. Minozzi S, Davoli M, Bargagli AM, Amato L, Vecchi S, Perucci CA. An overview of systematic reviews on cannabis and psychosis: discussing apparently conflicting results. *Drug Alcohol Rev*. 2010;29(3):304-317.
45. Proal AC, Fleming J, Galvez-Buccollini JA, Delisi LE. A controlled family study of cannabis users with and without psychosis. *Schizophr Res*. 2014;152(1):283-288.

46. Goodman SE, Leos-Toro C, Hammond D. Risk perceptions of cannabis- vs. alcohol-impaired driving among Canadian young people. *Drugs: Education, Prevention and Policy*. 2019;1-8. doi:10.1080/09687637.2019.1611738
47. Nutt DJ, King LA, Phillips LD. Drug harms in the UK: a multicriteria decision analysis. *The Lancet*. 2010;376(9752):1558-1565. doi:10.1016/s0140-6736(10)61462-6
48. Lachenmeier DW, Rehm J. Comparative risk assessment of alcohol, tobacco, cannabis and other illicit drugs using the margin of exposure approach. *Sci Rep*. 2015;5:8126.
49. Faber MS, Jetter A, Fuhr U. Assessment of CYP1A2 activity in clinical practice: why, how, and when? *Basic Clin Pharmacol Toxicol*. 2005;97(3):125-134.
50. Sativex Oromucosal Spray - Summary of Product Characteristics (SmPC) - (emc). <https://www.medicines.org.uk/emc/product/602/smpc>. Accessed October 23, 2019.
51. Hartman RL, Brown TL, Milavetz G, et al. Controlled Cannabis Vaporizer Administration: Blood and Plasma Cannabinoids with and without Alcohol. *Clin Chem*. 2015;61(6):850-869.
52. Hollister LE. Interactions of cannabis with other drugs in man. *NIDA Res Monogr*. 1986;68:110-116.
53. Iffland K, Grotenhermen F. An Update on Safety and Side Effects of Cannabidiol: A Review of Clinical Data and Relevant Animal Studies. *Cannabis Cannabinoid Res*. 2017;2(1):139-154.
54. Yamaori S, Okamoto Y, Yamamoto I, Watanabe K. Cannabidiol, a major phytocannabinoid, as a potent atypical inhibitor for CYP2D6. *Drug Metab Dispos*. 2011;39(11):2049-2056.
55. Institute of Medicine (US), Joy JE, Watson SJ Jr, Benson JA Jr. *First, Do No Harm: Consequences of Marijuana Use and Abuse*. National Academies Press (US); 1999.
56. Neavyn MJ, Blohm E, Babu KM, Bird SB. Medical marijuana and driving: a review. *J Med Toxicol*. 2014;10(3):269-279.
57. Elvik R. Risk of road accident associated with the use of drugs: a systematic review and meta-analysis of evidence from epidemiological studies. *Accid Anal Prev*. 2013;60:254-267.
58. Asbridge M, Hayden JA, Cartwright JL. Acute cannabis consumption and motor vehicle collision risk: systematic review of observational studies and meta-analysis. *BMJ*. 2012;344:e536.
59. Health Canada. Talk about cannabis - Canada.ca. <https://www.canada.ca/en/health-canada/services/drugs-medication/cannabis/resources.html?health-care-professionals>. Published May 11, 2018. Accessed October 23, 2019.
60. Harm Reduction, Health Promotion, and Cannabis Screening tools | Canadian Public Health Association. <https://www.cpha.ca/harm-reduction-health-promotion-and-cannabis-screening-tools>. Accessed October 23, 2019.
61. Health Canada. Canada’s lower-risk cannabis use guidelines - Canada.ca. <https://www.canada.ca/en/health-canada/services/drugs-medication/cannabis/resources/lower-risk-cannabis-use-guidelines.html>. Published May 10, 2019. Accessed December 11, 2019.
62. Scope of Practice for Naturopathic Physicians: Standards, Limits and Conditions for Prescribing, Dispensing and Compounding Drugs. <http://www.cnpbc.bc.ca/wp-content/uploads/Scope-of-Practice-for-Naturopathic-Physicians-SLC-for-Prescribing-Dispensing-and-Compounding-Drugs-2018-10-16.pdf>. Accessed December 11, 2019.
63. College of Naturopaths of Ontario. Prescribing. http://www.collegeofnaturopaths.on.ca/CONO/Members_Practice/Prescribing_Drugs/What_NDs_can_Prescribe/CONO/Members_Practice/Controlled_Acts/Prescribing.aspx?hkey=303aac21-724b-4170-a786-755174859941. Accessed December 11, 2019.
64. Advanced Solutions International, Inc. New Guideline: Non-medical (Recreational) Cannabis. http://collegeofnaturopaths.on.ca/CONO/NEWS/New_Guideline_Non-medical_Recreational_Cannabis.aspx. Accessed October 23, 2019.
65. Turner SD, Spithoff S, Kahan M. Approach to cannabis use disorder in primary care: focus on youth and other high-risk users. *Can Fam Physician*. 2014;60(9):801-808. e423-e432.
66. CDC’s Office on Smoking, Health. Smoking and Tobacco Use; Electronic Cigarettes. October 2019. https://www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-disease.html. Accessed October 23, 2019.
67. Lewis N. E-cigarette Use, or Vaping, Practices and Characteristics Among Persons with Associated Lung Injury — Utah, April–October 2019. *MMWR Morb Mortal Wkly Rep*. 2019;68. doi:10.15585/mmwr.mm6842e1
68. Kowitz SD, Osman A, Meernik C, et al. Vaping cannabis among adolescents: prevalence and associations with tobacco use from a cross-sectional study in the USA. *BMJ Open*. 2019;9(6):e028535.