

Priorities for a Comprehensive Post-Legalization Cannabis Research Agenda in Canada

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The Canadian cannabis regulatory environment has been highly dynamic over the last 5 years. Access to medical cannabis further increased via the implementation of the *Access to Cannabis for Medical Purposes Regulations* in 2016; the Trudeau government was elected in 2015 on a platform that included recreational cannabis legalization; and, on October 17, 2018, *The Cannabis Act* came into force, legalizing recreational cannabis nationwide. Indeed, the landscape continues to be dynamic, as policy changes continue to take effect (e.g., availability of storefront access, edible products). Within this context, there is widespread recognition of the need for more research on cannabis use and misuse in Canadian society. Setting a research agenda, however, is challenging because of the multifarious nature of cannabis. The plant itself is highly diverse chemically, containing over 500 constituents of which more than 100 actively affect the body's endocannabinoid system.¹ It can be consumed in a variety of different ways (e.g., inhalation, oral, oromucosal, topical) and it is used for both recreational and medical purposes. Finally, the risks and potential benefits of cannabis do not fall evenly across the Canadian population. Thus, identifying priorities quickly runs the risk of “blind men and the elephant” problem, in which what matters most can look very different from disparate vantage points.

To avoid this problem, this commentary seeks to step back and take a broad perspective on a comprehensive research program on post-legalization cannabis use and misuse in Canada. The focus is intentionally breadth over depth and, as a framework, I propose that such an undertaking should be thought of as a matrix, with substantive research topics being thought of as “horizontal” categories and important subpopulations as inter-

secting “verticals.” In other words, we need to identify the critical questions that require answers and how these answers are particularly pertinent to certain groups in Canadian society. The initial sections will focus on the major content areas, the horizontals, followed by a consideration of the critical subpopulations, the verticals.

MEASUREMENT PRIORITIES

A number of foundational priorities can be broadly grouped into issues of measurement. This includes epidemiological research surveilling the prevalence of cannabis use and misuse over the course of legalization and subsequent policy changes. Beyond simply prevalence and level of consumption, however, there are a number of subordinate surveillance priorities, such as changes in the types of products Canadians are using, changes in the composition of the products themselves (both legal and contraband), and changes in consumer knowledge and perceptions of cannabis products.

A second foundational measurement issue is establishing valid biomarkers of cannabis consumption to inform law enforcement and high-risk occupational settings. The psychoactive ingredient in cannabis, Δ -9-tetrahydrocannabinol (THC), is highly lipophilic, meaning that it is readily absorbed into adipose tissue. Over time, THC gradually leeches back into the bloodstream and other body fluids, resulting in its long window of detection. This is in stark contrast to alcohol, where breath alcohol is directly correlated with alcohol in the bloodstream and level of impairment. Although advances are being made, there are no current devices that are considered “gold standards” in the way that breathalyzers are for alcohol and establishing equivalent valid biomarkers is a very high priority.

RISKS AND HARMS

A second domain of research priorities can be broadly categorized as understanding the adverse consequences of cannabis use, including both acute and chronic risks and harms. With regard to acute risks, a very high priority is understanding the extent to which cannabis use leads to acute cognitive impairment that puts an individual at-risk

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for a car accident, a fall, or another adverse consequence of intoxication. This directly pertains to the preceding measurement issue insofar as there is a need for valid assays to consumption, but also valid cutoffs that reflect impairment. This is a controversial issue, as cannabis has been shown to produce performance decrements in driving simulators but the extent to which this translates into real-world risk is not clear.² The other acute risk that warrants greater investigation is overdose. Although cannabis does not have a known lethal dose, overconsumption resulting in cannabis-induced psychosis or delirium is certainly possible, especially via edible products, and these outcomes are substantially understudied.

Beyond acute risks, there are a number of adverse consequences of chronic cannabis consumption. It is a common myth that cannabis is not addictive and the Canadian lifetime prevalence of cannabis use disorder (CUD), the formal psychiatric diagnosis for addiction to cannabis, is 7%.³ In terms of its abuse liability, in a large epidemiological study, 9% of individuals who reported ever using cannabis developed CUD, a rate that was lower than the parallel one for cocaine, alcohol, and tobacco.⁴ Importantly, however, misuse of cannabis at subclinical levels is still associated with risk for harm⁵ and there is no established safe level of use.⁶ Furthermore, cannabis use has been linked to greater risk for other psychiatric disorders also. There is a well established link between cannabis use and psychosis, although the mechanisms are not well understood and the causal directionality is ambiguous.⁷ Cannabis use is also associated with depression and anxiety, and longitudinal studies have shown it predicts worsening of these conditions over time.⁸ Beyond its well-established acute effects on cognition, there is emerging evidence of cognitive consequences that persist over time or may in fact be permanent.⁹ Recent studies suggest these effects are restricted to when THC is still detectable in urine,¹⁰ but illuminating the specific areas of cognitive impairment and trajectories of recovery (or lack thereof) is a high priority.

Risks from chronic cannabis use extend beyond the brain also. The most common route of administration is inhalation and understanding the effects on respiratory system is a high priority. Cannabis use has been shown to be associated with chronic bronchitis,¹¹ but many questions remain about other lung harms and how alternative routes of administration (e.g., vaping) may alter the associated risks. The gastrointestinal system is implicated in an unusual condition associated with chronic cannabis use, cannabinoid-induced hyperemesis syndrome, which as its name implies is associated with chronic vomiting, among other symptoms. The syndrome is transiently alleviated by very hot

showers and remains poorly understood, but its prevalence appears to be getting higher.¹² Finally, there is a high need for more research on cannabis use during pregnancy, which has been associated with preterm birth and other adverse consequences.¹³ This is particularly troubling because of the comparatively small evidence base and a recent study finding that 69% of dispensaries actually recommended cannabis for morning sickness.¹⁴

The essential complement to investigations of adverse consequences is clinical research to reduce risks and harms from cannabis. This represents a broad portfolio of research topics, including public education efforts, prevention of underage cannabis use, and intervention research, which itself comprises a range of foci, from brief interventions to extended treatments. The best evidence is in support of psychological interventions for treating CUD¹⁵ and further research to optimize existing psychological approaches is needed. Unlike alcohol use disorder or opioid use disorder, there are no Health Canada-approved medications for CUD currently, necessarily making it a priority area.

THERAPEUTIC APPLICATIONS OF CANNABIS

There has been a dramatic increase in the number of Canadians using cannabis for medicinal purposes. As shown in Figure 1, the number of Canadians registered as medical cannabis users increased from less than 8000 in 2014 to over 340,000 in 2018, an increase of more than 4000%. This increase was not because of a commensurate increase in the evidence of efficacy. Currently, there is moderate quality evidence that cannabis is useful for pain, spasticity in multiple sclerosis, and chemotherapy-induced nausea.¹⁶ More recently, randomized controlled trials have also indicated that cannabidiol, a nonpsychoactive cannabinoid, is effective in treating rare pediatric seizure disorders.²⁰ For many conditions, the evidence is at best correlational or anecdotal.¹⁷ For example, medical cannabis patients commonly report using cannabis for anxiety and depression, but the strength of the evidence of efficacy for those conditions is minimal.¹⁸ Sleep is a promising candidate, but has primarily been investigated as secondary outcome in the context of treating other conditions.¹⁹ Cannabidiol is a promising candidate for alcohol use disorder, but again virtually all of the research is preclinical.²⁰ Fundamentally, at a field level, there is a high need for more experimental human research investigating the effects of cannabis and its constituents, especially randomized controlled trials that directly test biologically active cannabis products against a placebo condition.

Registered Medical Cannabis Users in Canada, 2014-2018

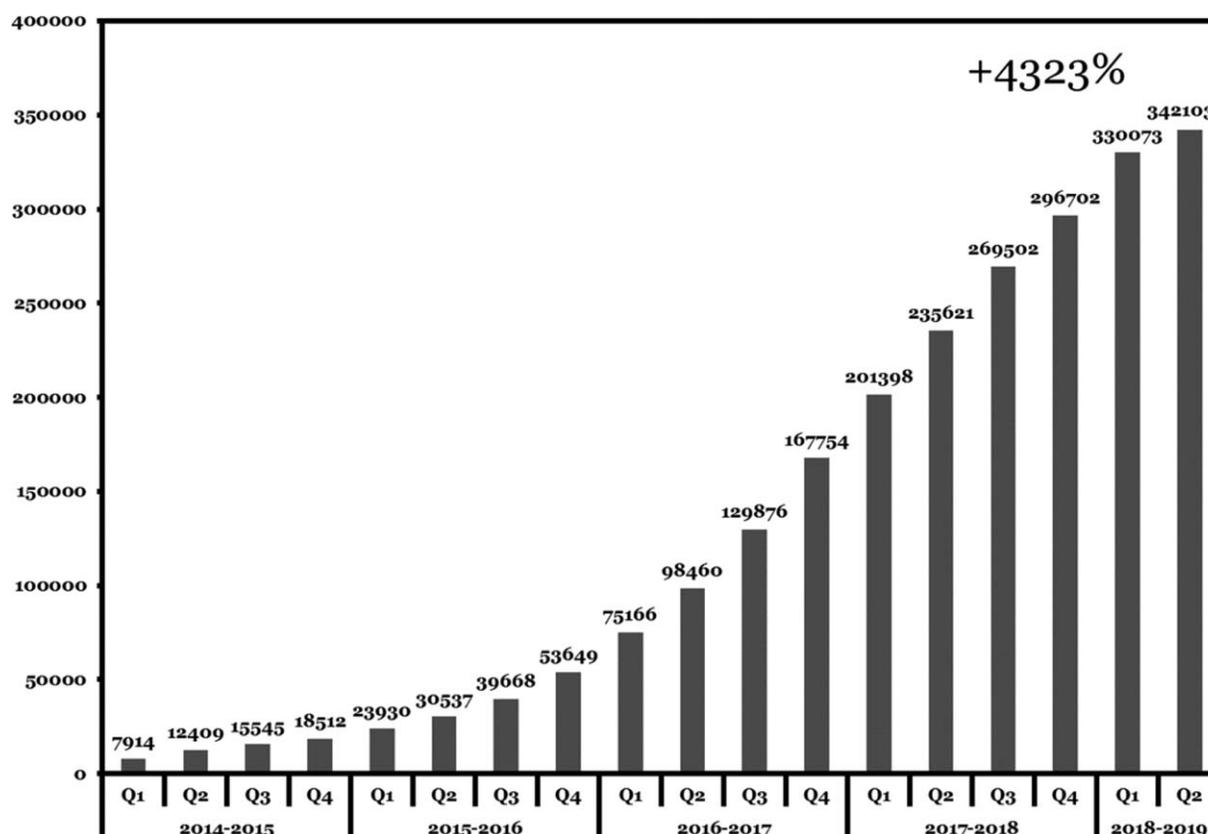


Fig. 1.

Registered medical cannabis users in Canada, 2014 to 2018. (Source: Health Canada.)

A further nuance to medical cannabis research is consideration of both clinical efficacy and the associated side effect profile, the Yin and Yang of a drug's therapeutic profile. For example, recent reviews of cannabis for pain have revealed unfavourable ratios of the number needed to treat (successfully) to the number needed to harm (in terms of side effects).²¹ Finally, cannabis has been speculated to be a substitute for other pharmaceutical products, but direct evidence is scant and observational findings cannot be definitive.²² Although there is great optimism for therapeutic applications of cannabis to a variety of conditions, major evidence gaps remain.

POLICY RESEARCH

At a higher level than individual harms or benefits, trenchant policy research will be essential. Legalization itself includes successive phases of regulatory change that warrant systematic examination. Differences in provincial and territorial laws create natural experiments, permitting, for example, comparisons between different access and distribution models. Similarly, systematically investigating pricing and taxation of cannabis will be warranted,²³ akin to alcohol and tobacco, the other legally regulated psychoactive drugs.

HIGH-PRIORITY SUBPOPULATIONS

In each of the preceding cases, the findings in an area may well differ across subpopulations within Canadian society and understanding these intersections is a high priority. To start, it is well established that there are sex differences in the endocannabinoid system and in relation to patterns of cannabis,²⁴ suggesting that sex should routinely be examined as a potential moderator of findings. Even when differences between males and females are not present, reporting evidence of parity is nonetheless worthwhile. Furthermore, beyond biological sex, routine consideration of gender identity is highly worthwhile from the perspective of inclusivity in research.

Two priority subpopulations can be defined from a developmental standpoint. Cannabis use typically initiates during adolescence and emerging adults (age 18–25) have the highest rates of cannabis misuse and CUD.²⁵ As such, young adults (broadly defined) are a high-priority population because that is when use starts and is heaviest. On the other hand, although seniors have the lowest cannabis use rates among adults, a steep rate of increase has been observed,²⁶ perhaps reflecting curiosity or optimism in medical cannabis.

Military veterans are also a high-priority subpopulation,²⁷ both because, by dint of their service, they disproportionately suffer from chronic pain and psychiatric condition; and because medical cannabis is reimbursed by Veterans Affairs Canada, facilitating access. Another group that may be disproportionately vulnerable to negative outcomes comprises individuals with psychiatric disorders, including other substance use disorders, who use cannabis at much higher rates than the general population and are at particularly high risk of adverse consequences.⁷ Other groups that warrant further examination are individuals who are racial or sexual minorities,^{28,29} and who may be more generally psychosocially disadvantaged by discrimination, stigma, and victimization. Finally, understanding the impact of legalization and, more broadly, cannabis use and misuse for Indigenous Canadians is a critical priority.³⁰ Further nuances apply to these subpopulations also, as, for example, indigenous individuals represent a number of highly heterogeneous subpopulations. Collectively, there is a high need to consider individual and subpopulation characteristics that bear on differential risks and benefits of cannabis across Canadians.

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CONCLUSIONS

This conceptual matrix of substantive research questions and priority subpopulations represents an attempt to identify critical domains in a post-legalization landscape comprehensively, to step back and view the full “elephant,” so to speak. Blindspots remain, no doubt, but even a high-level consideration nonetheless reveals how multifarious the potential risks and benefits are to Canadian society. Across these many questions, it will be essential to prioritize critical thinking, objectivity, and methodological rigour, to use this national natural experiment as a unique opportunity to advance both the science of cannabis and Canadian public health.

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