Cannabis Research in Urgent Priority Areas End-of-Grant Virtual Workshop

EXECUTIVE SUMMARY

In partnership with:

Canadian Centre on Substance Use and Addiction
Centre canadien sur les dépendances et l’usage de substances

Mental Health Commission of Canada
Commission de la santé mentale du Canada
Canadian Institutes of Health Research

At the Canadian Institutes of Health Research (CIHR), we know that research has the power to change lives. As Canada's health research investment agency, we collaborate with partners and researchers to support the discoveries and innovations that improve our health and strengthen our health care system.

CIHR Institute of Neurosciences, Mental Health and Addiction

The CIHR Institute of Neurosciences, Mental Health and Addiction (CIHR-INMHA) invests in fundamental and clinical research on the brain and spinal cord to enhance the understanding of cognitive, emotional and sensorimotor functions. Advances in these areas will ensure a brighter future for Canadians living with neurological and mental health conditions.
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Executive Summary

When cannabis for non-medical use was legalized in Canada on October 18, 2018, there remained many unknowns about the health and safety effects of cannabis use, as well as the behavioural, social, ethical and economic implications of legalization. While the field of cannabis-related research is broad, a number of urgent priority areas were identified through focused consultations led by the Canadian Institutes of Health Research (CIHR). Identified priority research areas included both the potential therapeutic benefit for specific indications including unresolved pain, and the potential risks of cannabis use in different populations.

The Catalyst Grant: Cannabis Research in Urgent Priority Areas funding opportunity was launched in July 2018 to expand cannabis research and build cannabis-related research capacity in the following urgent priority areas:

- Neurodevelopment;
- Prevention, harm reduction and treatment of problematic cannabis use;
- Potency and product safety;
- Social determinants of health and key populations;
- Mental health;
- Cannabis and other drug / substance use; and
- Cannabis and pain management.

CIHR, the Mental Health Commission of Canada (MHCC) and the Canadian Centre on Substance Use and Addiction (CCSA), through CIHR's Integrated Cannabis Research Strategy (ICRS), invested over $3 million to support 26 research projects.

In November 2020, CIHR, MHCC and CCSA hosted a three-day virtual end of grant workshop bringing together researchers, policy makers, community members, people with lived and living experience, partners and other knowledge users. The objectives of the Cannabis Research in Urgent Priority Areas End of Grant Virtual Workshop were to:

- Inform the development of future, larger-scale research projects related to the potential benefits or harms of cannabis and its use
- Support linkages and collaborations amongst funded research teams and stakeholders to increase research impact
- Share, and promote the uptake of evidence to inform ongoing and future development of policies, practices and programs related to cannabis
- Facilitate knowledge translation among knowledge users, stakeholders and researchers

Each of the 26 project teams provided a brief summary of their work, including relevance and key findings. Their presentations were categorized into three sessions: Brain and Behavioural Effects of Cannabis, Cannabis-related Harms and the Continuum of Care, and Medical or Therapeutic Use of Cannabis. Each session was followed by a panel discussion, where panelists shared their reflections on the findings presented and the potential implications of the research on their own work or community.

The workshop provided a forum for rich discussions and interactions between researchers and knowledge users. There is growing evidence on both the health risks and benefits of cannabis use, but significant gaps in knowledge persist, or are becoming evident.

SUMMARY OF KNOWLEDGE GAPS AND RECOMMENDATIONS

The need for more research on cannabis use by older adults was discussed. Specifically, understanding the harms of cannabis use in this population, as well as potential medical benefits in areas such as pain and sleep.

Researchers were encouraged to recognize the complexity and diversity of youth populations. Attempting to understand the culture and context of cannabis use in youth, and how including youth in the research design process and knowledge mobilization could help increase the impact and relevance of research findings for this population.
Researchers discussed the challenges they have faced in carrying out clinical research with cannabis including the ability to source a cannabis product for use in their studies, and the process of obtaining a No Objection Letter in response to a Clinical Trial Application.

Both researchers and stakeholders expressed the need for significant efforts to be made for clinical research findings to be disseminated to the public through targeted education campaigns, and for guidance and training to be developed for physicians.

Finally, the COVID-19 pandemic has had an impact on cannabis research and cannabis use in Canada. Many researchers noted significant delays in recruitment and data collection, and challenges with pivoting to online methods. Preliminary data suggests that cannabis use may have increased during the pandemic and supply chain disruptions may have impacted access. More research is needed to better understand these effects.

Building on the research capacity and evidence generated through the Cannabis Research in Urgent Priority Areas catalyst grants, CIHR and partners continue to support research to inform policy, therapeutic practice, harm reduction and prevention efforts through the Integrated Cannabis Research Strategy.
Project Summaries
New metabolomics technologies to characterize cannabis safety and potency

NOMINATED PRINCIPAL INVESTIGATOR(S)

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KEY MESSAGES

We have characterized six different strains of commercial cannabis using advanced metabolomics techniques. In total we have identified more than 1,200 different compounds using mass spectrometry techniques. Another 500 have been fully quantified using these newly developed assays. We have also developed robust analytical methods to detect more than 30 cannabinoids in human biofluids. In addition to this analytical work we have conducted a comprehensive literature analysis on the chemical composition of cannabis and have compiled detailed chemical, biological, biochemical and spectroscopic data on more than 6,200 different cannabis compounds from more than 100 different cannabis varietals. The information is contained at the cannabis compound database which is located at www.cannabisdatabase.ca

ISSUE

Our understanding of the chemical composition of cannabis is very limited. However, cannabis chemicals have a profound effect on its safety and efficacy. We don’t know what cannabis compounds are harmful, what compounds are helpful and we don’t even know how abundant those chemicals are in certain commercial strains of cannabis. There is an urgent need to provide detailed chemical compositional information about commercial cannabis varieties and to provide information about the biochemical or biological effects that these compounds may have on humans. There is also a need to develop methods that can readily and accurately measure cannabis constituents (in commercial cannabis varieties) and detect key cannabinoids in human biofluids.

AIM

Our aim was to comprehensively characterize nearly all of the detectable chemicals in cannabis using a technique called “metabolomics.” Metabolomics is a technique that employs advanced analytical chemistry instruments to identify and quantify large numbers of chemicals or metabolites in cells, tissues and extracts. Metabolomics can also be used for the identification, quantification and characterization of a wide range of chemicals found in plant tissues and plant extracts (i.e., oils or tinctures). This work will allow us to develop fast and simple methods to measure different types of chemicals in cannabis (or used in the cannabis production process) to maximize benefit and minimize harm. We also intended on using these metabolomic tools to characterize the effects of different cannabis strains with regard to safety and potency on rats.

STUDY DESIGN

The study involved three components or phases. The first phase involved constructing a comprehensive cannabis reference metabolome using a combination of experimental, literature review and computational efforts. The second phase involved developing quantitative metabolomic assays for the rapid quantification of key cannabis compounds from various cannabis strains or products. The third phase involved using the knowledge and methods developed in the first two phases to assess the safety and potency of different cannabis strains or products using a rat behaviour model. This final phase, which is still under development, involved the identification of doses that cause behavioural changes and cognitive impairment in healthy rats following administration of oil extracts from different cannabis strains. This will involve assessing runway walking, open field activity, sucrose preference, general locomotor ability and rotarod testing among the rats and using metabolomics methods to assess the levels of cannabinoids in the rats after (and during) the tests.
FINDINGS

We have comprehensively characterized six different strains of commercial cannabis using advanced metabolomics techniques. In total we identified more than 1,200 different compounds using untargeted mass spectrometry techniques. Another 500 have been fully quantified using these newly developed assays. We have also developed robust analytical methods to detect more than 30 cannabinoids in human or mammalian biofluids. In addition, we have conducted a comprehensive literature analysis on the chemical composition of cannabis and have compiled detailed chemical, biological, biochemical and spectroscopic data on more than 6,200 different cannabis compounds from more than 100 different cannabis varietals. The information is contained at the cannabis compound database which is located at www.cannabisdatabase.ca

IMPLICATIONS

Our study has created data resources on cannabis (or cannabis products) and on the health/biological effects of cannabis that can be freely used by the Canadian public. This resource is located at www.cannabisdatabase.ca. This resource will provide Canadians with up-to-date, detailed information on cannabis constituents and their beneficial and/or adverse health effects. In addition, we have developed robust metabolomic assays that permit the accurate detection and quantification of hundreds of cannabis compounds from tiny amounts of cannabis material. These methods will be published in top tier journals at the end of 2020 and will be made available to cannabis characterization laboratories around the world. This information and these tools will play important roles in assessing the safety and potency of commercial cannabis products.
A pilot prospective cohort study to examine the prenatal cannabis exposure and early developmental outcomes

NOMINATED PRINCIPAL INVESTIGATOR(S)

Hamideh Bayrampour, UBC

KEY MESSAGES

We experienced lots of delays in starting this project; we were informed that we received the funding for the project in mid-March 2019. We started the ethics application right away and we worked several months with the BC Women’s Hospital ethics board and finally received their approval in October 2019. Meanwhile, we worked with BC Women’s Hospital Program Utilization Unit and received their approval in February 2020. While we were working the Pathology Unit BC Women’s Hospital, the pandemic emerged and all research activities stopped. We applied in June to restart our project and received permissions at the end of September. We will start data collection this week. Fortunately, we received the automatic extension of the project due to the pandemic.

ISSUE

This pilot feasibility project includes several sections and disciplines: lab sciences, clinical units and self-report surveys. We found that coordinating all these sections is very time consuming, particularly because some units and sections often did not work parallel to each other. For example, the labour and delivery unit did not review our application in depth until we received the final ethics approval. In our experience, to conduct this project in a large scale or similar multidisciplinary projects that includes several clinical and lab units more time should be allocated to obtain relevant approvals. Also, in general, a more coordinated approach among these sections can be extremely helpful in facilitating conduct of multidisciplinary research with clinical and biomedical parts.

AIM

In this pilot project we proposed to:

1) examine the feasibility and acceptability of conducting a large prospective cohort study and

2) explore the clinical utility of testing a fetal specimen, i.e., umbilical cord tissue, to detect and quantify in utero cannabis exposure.

STUDY DESIGN

Pilot prospective cohort study

FINDINGS

Aim 1: We found the process of receiving required approvals very long and complicated. As noted in the above section, in our experience, to conduct this project in a large scale or similar project that includes several clinical and lab sections more time should be considered to obtain relevant approvals. Also, in general a more coordinated approach among these sections can be extremely helpful in facilitating conduct of multidisciplinary research with clinical and biomedical parts in general. Additionally, the ethics review process was complicated due to the involvement of substance use during pregnancy. The data collection for participant perspectives is underway.

Aim 2: Study is ongoing.

IMPLICATIONS

As noted in the above section, in our experience, to conduct this project in a large scale or similar project that includes several clinical and lab sections more time should be considered to obtain relevant approvals. Also, in general a more coordinated approach among these sections can be extremely helpful in facilitating conduct of multidisciplinary research with clinical and biomedical parts in general. Additionally, the ethics review process was complicated due to the involvement of substance use during pregnancy.
Double jeopardy: Effects of prenatal cannabis and ethanol exposure on hippocampus structure and function

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ISSUE
With the relaxation of cannabis restrictions across North America, a growing proportion of young adults (19-30 years of age) are reporting the simultaneous use of alcohol and marijuana (SAM), and indications are that this trend will continue to rise. The age demographics (19-30 years) also coincide with the peak fertility period for females, and it is known that SAM significantly increases the risk of unplanned pregnancies. Moreover, the use of illicit drugs in this age group is common, with cannabis being the most commonly used drug by pregnant women. Approximately half of cannabis users also report alcohol use. Although the prevalence rates for SAM are likely to rise, the effects of combined prenatal ethanol exposure and THC (delta9-tetrohydrocannibol) exposure on the developing brain are not well understood.

AIM
This proposal is geared to assess the role of prenatal cannabinoid exposure on synaptic plasticity in the hippocampus formation, a brain region intimately tied to learning and memory processes.

STUDY DESIGN
Pregnant dams are exposed to either ethanol or THC alone, or in combination, throughout gestational days three to 20. Animals generally will give birth on day 21-22. The offspring are then assessed for changes in synaptic plasticity during adolescence (post-natal days 28-35), a time when bidirectional synaptic plasticity is usually maximal in the hippocampal formation. Separate cohorts are also used to examine structural changes in the brains during adolescence.

FINDINGS
The study is still ongoing due to delays introduced by both the licensing process and the COVID-19 pandemic.

IMPLICATIONS
This work will enable us to determine how prenatal exposure to THC, ethanol, or a combination of the two, can impact the developing hippocampus, an area of the brain critical for normal learning and memory performance.
Effects of perinatal cannabinoids exposure on long-term
cognition and memory

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KEY MESSAGES
We have demonstrated that fetal exposure to either THC or CBD leads to a reduction in the fetal placental weight ratio, an indice of placental insufficiency. We have also demonstrated the THC-exposed offspring exhibit defects in pancreatic beta cell mass, CVD function, and neurobehavioural outcomes in a sex-specific manner.

ISSUE
The urgent priority was to assess the impact of the legalization of cannabis in Canada in our pregnant population — both short and long-term on memory and cognition in exposed children.

AIM
The aims of the study were to:
(1) determine if Δ9-THC exposure with or without CBD during perinatal life leads to the development of fetal growth restriction leading to an impairment of hippocampal-mediated cognitive/memory processing
(2) identify the developmental windows (e.g., gestation, lactation or both) when Δ9-THC exposure has an irreversible adverse impact on memory and cognition long-term
(3) elucidate the role of peroxisome proliferator receptors (PPARδ, PPARα, and PPARγ) and their associated epigenetic mechanisms in mediating the adverse effects of perinatal Δ9-THC exposure on neuronal development in the brain.

STUDY DESIGN
We used the well-established rat model of THC-exposure in pregnancy. We have pregnant rats either THC (3 mg/kg/day) or CBD (30 mg/kg/day) from gestational day six to term (GD22). We assessed maternal-fetal outcomes, and metabolic outcomes (heart function, glucose tolerance tests, lipids, steroid hormone levels) in four months male and female offspring. We also performed neurobehavioural tests for cognition, memory and anxiety.

FINDINGS
To date, we have found that CBD or THC leads to fetal growth restriction. Female THC offspring specifically exhibit glucose intolerance, anxiety and depression. Male offspring exhibit defects in memory, anxiety, cardiovascular defects and higher hepatic triglycerides.

IMPLICATIONS
These studies address the paucity of information regarding if exposure to THC or CBD is ‘safe’ in pregnancy —short and/or long-term. They imply that cannabis in pregnancy has long-term adverse implications on postnatal metabolic health and neurobehaviour.
A scoping review to assess the effects of medical and non-medical cannabis use in older adults

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KEY MESSAGES
Based on our systematic scoping review of 95 studies, while data suggest cannabis may offer some benefits to older adults for managing symptoms associated with certain medical conditions (e.g., cancer-related pain), the benefit-risk ratio is unclear. In other conditions (e.g., Parkinson’s disease), the benefit and risk are unclear. Adverse events (AEs) were not routinely evaluated. Potential benefits were supported by limited data and must be balanced with risks of AEs. Data regarding pharmacokinetics, brain outcomes and the effects of non-medical use were sparse, as were data related to people with comorbidities. Future studies on older adults are needed.

ISSUE
Prior to its legalization, cannabis was the most commonly used illicit drug in those 50 years and older. While older adults most frequently report use of alcohol, nicotine and prescription drugs, cannabis rates have been increasing since October 2018. Older adults who use cannabis may represent those who have done so since adolescence, as well as those who began use later in life due to social isolation, comorbidities or other reasons. With legalization of non-medical cannabis in Canada, an increase in the frequency of medical and non-medical use of cannabis in older adults is likely. There is a need to be aware of unique effects it may possess.

AIM
Given slower metabolism, increased likelihood of polypharmacy, cognitive decline, chronic medical and mental health problems and sudden lifestyle changes (e.g., time of transition), there is potential for unique health effects of cannabis in older adults. We conducted a systematic scoping review of the literature to collate evidence regarding the effects of medical and non-medical cannabis use in older adults. We also sought to gather evidence to establish whether there was evidence of different effects in older adult subgroups related to existing health comorbidities, use of other substances, and method of cannabis consumption.

STUDY DESIGN
A systematic scoping review was performed using established methods outlined by the Joanna Briggs Institute. An information specialist designed a systematic search of the literature. Reviewers screened citations and full texts derived from the search to carry out study selection. Reviewers then performed data extraction from the set of included studies to compile data related to the health effects of cannabis in the older adult population. Tables, graphics and descriptive synthesis were used to summarize evidence in different populations/conditions and to identify evidence gaps. Inspection by type of cannabis use (e.g., medical, non-medical) and subgroups of interest (e.g., sex/gender, age groupings) was also planned. We identified 95 studies meeting selection criteria that included 17 systematic reviews, 31 RCTs and 47 non-randomized studies.

FINDINGS
Most studies focused on medical, rather than non-medical, cannabis use. Studies reported on mental and physical outcomes; data related to brain and pharmacokinetic outcomes were sparse. While data suggest cannabis may offer some benefits to older adults for managing some symptoms associated with certain medical conditions (e.g., cancer-related pain), the risk-benefit ratio is unclear. In other conditions (e.g., Parkinson’s disease), benefits and risks are unclear. AEs were not routinely evaluated. Potential benefits were supported by limited data, and must be balanced with risks of AEs. Studies on cannabis use for medical reasons unsupervised by a prescriber were sparse.
IMPLICATIONS

While data suggested medical cannabis may be beneficial for managing some symptoms associated with certain medical conditions in older adults, the benefit-risk ratio is unclear. In other conditions, neither the benefits nor risks are clear. There remain unknowns regarding pharmacokinetic and brain outcomes, and physical and mental effects in clinically important subgroups, including those with comorbid physical and mental health conditions, those using other substances, and those using different methods of cannabis consumption. Studies focused specifically on older adults were rare, and the effects associated with non-medical use were rarely studied. Future studies to address these gaps should be supported.
Parental cannabis use in the perinatal period and child outcomes: Capturing changes with legalization in the Ontario Birth Study

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KEY MESSAGES
Cannabis use very early in pregnancy may increase the risk of a smaller baby, even after accounting for many other factors. Many children are living in households where someone smokes or vapes cannabis and it is not known whether this exposure may affect child development.

ISSUE
Neurodevelopmental outcomes associated with cannabis use

AIM
1) to compare the prevalence of reported periconception and pregnancy cannabis use before and after legalization and examine factors associated with reported use
2) to determine the prevalence of early childhood second-hand exposure at eight months, 24 months and 36 months and examine factors associated with exposure
3) to obtain preliminary estimates of the association between periconception and/or pregnancy cannabis use and birth weight and size for gestational age
4) to obtain preliminary estimates of association between periconception, pregnancy, and postnatal exposure and measures of neurodevelopment at four years.

STUDY DESIGN
The Ontario Birth Study (OBS) is an open cohort where women are recruited early in pregnancy and followed until shortly after birth. The OBS study procedures are integrated with clinical care. Medical record information is collected for the study. Recruitment has been ongoing since 2013 with several hundred women recruited each year. The child follow-up component, OBS-Kids, continues to follow mothers and children in the OBS by telephone interview at eight months and 36 months and home visits at 24 months and four years. Questionnaires are administered at three time points in OBS (early pregnancy, late pregnancy and postnatal), and at all four time points in OBS-Kids. Information on maternal cannabis use is collected for the time around conception and during pregnancy and on household use during childhood. Information on many other factors is also collected.

FINDINGS
Reported cannabis use around conception in the OBS increased over time, beginning prior to legalization. Few women reported use during pregnancy. Cannabis use was associated with alcohol, tobacco, and prescription pain medication use, although most women who used cannabis did not report using any of these during pregnancy. Cannabis use around the time of conception was associated with a slightly lower birth weight and an increased risk of a small for gestational age infant, even after accounting for many other factors. During follow-up about 15% of mothers reported that someone in the household smoked or vaped cannabis.

IMPLICATIONS
The association of cannabis use early in pregnancy with adverse birth outcomes suggests that women who are planning a pregnancy should be counselled regarding these potential risks and cannabis should not be assumed to be harmless. There is also a need for studies of the relationship of second-hand exposure of children to cannabis smoke or vapour as well as exposure in early pregnancy with child neurodevelopment.
Friend or foe: Cannabis and the brain — from safety analysis to medical applications

NOMINATED PRINCIPAL INVESTIGATOR(S)
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KEY MESSAGES
New high-CBD C. sativa cultivars harbor profound anti-inflammatory potencies and are safe as they do not exert any major negative effects on the brain and behaviour of directly exposed animals.

ISSUE
CBD is a potent antioxidant and anti-inflammatory molecule with great therapeutic potential. There is an urgent need for new robust strains, especially those high in CBD with established proven medicinal properties and safety profiles. To address this urgent issue, we analysed medicinal properties of high-CBD strains and their safety profiles. We aimed to answer the following questions: What medicinal properties do these strains have? Do they cause any potential adverse effects? How do they affect the central nervous system (CNS)?

AIM
The overarching goal of our study was to understand molecular, cellular and anti-inflammatory effects, as well as neuroanatomical and behavioural effects, of the new high CBD cannabis extracts and to establish their CNS safety profiles. We aimed to dissect molecular, cellular, anti-inflammatory, behavioural and neuroanatomical effects as a function of sex, age and dose.

STUDY DESIGN
We analyzed the effects of cannabis extracts with 1:20 ratio of THC to CBD in a Long Evans rat model. In our preliminary experiments, these extracts demonstrated strong activity in the reduction of UVC- and LPS-induced inflammation in 3D human tissues. For the study, cannabis extracts were mixed with peanut butter and administered orally for 10 days. Our analysis focused on the hippocampus (HPC) and prefrontal cortex (PFC) based on their roles in memory, learning and executive functions. We analyzed molecular changes as a function of extract, age and sex. In collaboration with Dr. Kolb and Dr. Gibb, we scrutinized neuronal morphology and number in the PFC and hippocampus of experimental animals. We will also analyze the behavioural outcomes using a battery of well-established behavioural tests that are sensitive to hippocampal and/or PFC injury.

FINDINGS
Tested cannabis sativa extracts demonstrated strong anti-inflammatory properties using a battery of cell line and 3D tissue models. Based on these results, these extracts were chosen for the in-depth studies of behavioural and neuroanatomy effects on the rats and in vitro pre-clinical molecular data. The behavioural data show that there were no negative effects on behaviour, nor any effects on body, brain and gonad weight. Extracts also did not exert any major neuroanatomical changes. Extracts did not cause DNA damage. Further molecular analyses are ongoing.

IMPLICATIONS
Establishments of the rodent safety profiles of new high-CBD anti-inflammatory C. sativa cultivars led to the development of a large-scale clinical outreach program, whereby we hope to bring these extracts into the clinic through RCTs. We have established several critical clinical collaborations and started reaching out to Health Canada and regulatory agencies in other countries to plan and conduct RTCs in aimed to ascertain the therapeutic potential of these new cannabis cultivars for autoinflammatory diseases, cancer and neurological disorders.
Impact of chronic cannabis oil self-administration on neural circuitry in human obesity: A fMRI study

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KEY MESSAGES
Obesity is a global health concern. Evidence shows an association between cannabis consumption and body weight. The aim of the study is to determine the effect of chronic self-administration of cannabis oil versus placebo oil on the brain reward circuitry in human obesity. A greater understanding of the effects of cannabis in the obese state may potentially inform the development of intervention strategies for obesity.

ISSUE
Obesity is a serious health problem which increases the likelihood of developing other life-changing medical conditions. Despite increasing knowledge about the neural and metabolic basis of obesity, the development of effective anti-obesity treatment strategies has been a challenge.

AIM
Evidence shows an association between cannabis consumption and body weight. The overall objective of the funded research was to determine the effect of chronic self-administration of cannabis oil versus placebo oil on the brain reward circuitry in human obesity. The primary aim of the clinical trial was to test for the first time the hypothesis that exposure to cannabis versus placebo-cannabis promotes weight loss in adults with obesity. The secondary aim for which this funding was received was to explore the effects of exposure to cannabis (vs. placebo) on brain responses to food/control stimuli.

STUDY DESIGN
This is a double-blind, randomized controlled trial. Obese participants (n=60) will be randomized to three treatment groups: low dose cannabis (n=20), high dose cannabis (n=20) or placebo (n=20). Subjects will self-administer cannabis oil or placebo oil orally, for a 12-week period. At baseline and weekly thereafter, body weight will be measured for the primary outcome analysis. Using the CIHR funds, participants will also undergo two Magnetic Resonance Imaging scans during the course of the trial.

FINDINGS
We experienced unanticipated barriers that have significantly delayed commencement of the trial. In particular, the proposed supplier of the cannabis oil was unable to supply the drug product, and thus we had to amend our clinical trial protocol to use a cannabinoid drug that is marketed in Canada (nabilone). As a result, study recruitment has not yet commenced. However, we are now nearly complete with our regulatory approvals, and we anticipate starting recruitment within the next few months.

IMPLICATIONS
The anticipated results of this study will potentially have important implications for the treatment of obesity and will provide much-needed insight of neural mechanisms underlying the obese state in human adults.
Cannabinoid hyperemesis syndrome: Evaluation of health burden and treatment strategies

NOMINATED PRINCIPAL INVESTIGATOR(S)
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KEY MESSAGES
Cannabis hyperemesis syndrome (CHS) occurs in a small subset of chronic users, typically after years of use. Sufferers are likely to have a cannabis use disorder.

ISSUE
Cannabinoid hyperemesis syndrome (CHS) is a poorly understood condition that is characterized by recurring episodes of vomiting and abdominal pain in chronic, daily users. It is emerging as a worldwide problem, seen typically in emergency departments (ED) and in gastroenterology (GI) practices. It is responsible for a significant healthcare burden due to its relapsing nature, and its prevalence may increase with wider use in a population. Unfortunately, very little data exist globally, and no Canadian data exist on the demographics of CHS sufferers. While abstinence is the generally accepted treatment, other treatments for those unable to abstain are lacking.

AIM
This study was divided into two sub-studies that were designed to answer three primary aims:
Aim 1. To characterize the patients suffering from CHS through a series of questionnaires including: symptoms, general and psychiatric health, quality of life, cannabis use, and demographics.
Aim 2. To understand if changes in cannabis consumption affect symptoms of CHS.
Aim 3. To understand if haloperidol is effective over a four-week period in treating the symptoms of CHS.

STUDY DESIGN
Aim 1: Cross-sectional survey. All cannabis users with upper gastrointestinal symptoms suggestive of CHS (physician-identified or self-identified) are approached for enrollment either by a clinician, through study posters, or through social media posts. Participants who agree to take part are invited to fill out online questionnaires.
Aims 2 and 3: Prospective observational trial. Up to 20 participants who complete Aim 1 are invited to participate and advised that cannabis abstinence or reduction may help improve their symptoms, but is not necessary for participation. From week zero to week eight, cannabis use, symptoms, and urine cannabis metabolites are tracked every two weeks (Aim 2). From week eight to week 12, participants are prescribed open-label haloperidol, 1mg twice daily orally. Symptoms and urine cannabis metabolites are measured every two weeks (Aim 3). The primary endpoint is the reduction in composite gastroparesis cardinal symptom index at four weeks.

FINDINGS
For Aim 1, 61 CHS subjects (mean age 33.2 ± 1.5, range 17-66) were recruited. Median duration of cannabis use was 10 years (range 1-51) with 85.2% using daily. In the previous year, 94% had been hospitalized for at least one attack of CHS. Median CUDIT-R score was 19 (IQR 7), with 59/61 (97%) scoring ≥12, suggesting a cannabis use disorder is present in the vast majority of CHS sufferers.
Recruitment for Aims 2 and 3 was significantly hampered by a number of factors, particularly the COVID-19 pandemic, and is ongoing via a grant extension into 2021.
IMPLICATIONS

This is the first study to report that the vast majority of patients with CHS meet criteria for cannabis use disorder, typically of long duration. Thus the generally accepted treatment strategy of complete abstinence may be unlikely to succeed without support for quitting in the community. Results for an open-label four-week trial of haloperidol on CHS symptoms are anticipated in 2021, and will hopefully inform management strategies and/or future controlled trials in this field.
Assessing the impacts of the Cannabis Act on patterns of motor vehicle collision injuries among youth and young adults in emergency departments across Canada

NOMINATED PRINCIPAL INVESTIGATOR(S)

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KEY MESSAGES

A number of public health experts and researchers expressed concern that cannabis legalization might increase traffic-related harms, especially among youth. Drawing upon emergency department records of from Ontario and Alberta (April 1, 2015-December 31, 2020), our study found that cannabis legalization (implemented on October 17, 2018 via the Cannabis Act) was not associated with any evidence of significant post-legalization changes in youth or adult patterns of emergency department visits for injuries due to motor vehicle collisions. In other words, Canada’s cannabis legalization was not associated with evidence of post-legalization increases (or decreases) in youth or adult traffic-related injuries seen in emergency departments in Ontario or Alberta.

ISSUE

There was a strong public health concern that cannabis legalization might increase traffic-related harms in Canadian society, especially among youth. The current study examined this issue.

AIM

The study aimed to assess the potential impacts of Canada’s cannabis legalization on patterns of motor vehicle collision injuries among youth and adults in Ontario and Alberta — two provinces with virtually 100% coverage of emergency department utilization in the population.

STUDY DESIGN

Utilizing emergency department records (April 1, 2015-December 31, 2019) obtained from the Canadian Institute for Health Information, the study employed Seasonal Autoregressive Integrated Moving Average (SARIMA) time series models to estimate the association between cannabis legalization (implemented on October 17, 2018) and patterns of motor vehicle collision injury presentations to emergency departments in Ontario (n = 417,942) and Alberta (n = 152,181). ICD-10 codes were used to identify injuries due to motor vehicle collisions. We stratified SARIMA models by province (Ontario, Alberta), age group [adults versus youth, with youth defined as individuals younger than the provincial minimum legal cannabis sales age (18 years in Alberta; 19 years in Ontario)], and sex (male, female). This stratification process yielded eight SARIMA models, each working upon weekly counts of ICD-10-defined motor vehicle collision presentations.

FINDINGS

Across all eight SARIMA models (each stratified by sex, age group and province), there was no evidence that cannabis legalization (enacted on October 17, 2018) was associated with evidence of any significant increases (or decreases) in post-legalization patterns of Ontario or Alberta emergency department injuries due to motor vehicle collisions.
IMPLICATIONS

At this time, the findings of the scant scientific literature on this topic are mixed: a few studies (based on US and Uruguayan data) have found some evidence of significant associations between cannabis legalization and increases in traffic-related deaths, while others have shown no evidence of associations between legalization and traffic fatalities. The current study adds to this literature and it provides important evidence about the potential impacts of cannabis legalization on a key public health outcome — morbidity due to motor vehicle collisions. Given the importance of this topic and the lack of scientific evidence on this issue, future research will need to assess this issue using other traffic-related outcomes.
Shared and specific risk factors for early onset cannabis and other substance use and later substance use disorders: Can we predict who will initiate cannabis use early and who will develop future substance use problems?

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KEY MESSAGES
Cannabis use (CU) during adolescence is associated with a range of problems, including higher risk for adult cannabis and other substance use disorders (SUDs). However, this risk varies by age of onset, and its interaction with other individual and environmental factors.

ISSUE
Cannabis use and other drug/substance use; cannabis use and mental health

AIM
The present project aimed to examine (1) whether the associations between age of onset of CU and SUDs remain over and above risk factors in childhood, adolescent and early adulthood; and (2) whether different cannabis use profiles, individual and environmental factors moderate the link between CU age of onset and later substance use problems, if any.

STUDY DESIGN
The design of the study is prospective longitudinal, in which we followed a cohort of youth from the Québec Longitudinal Study of Child Development (QLSCD; first cohort). This cohort was previously followed from five months of age until 18 years, and was designed to assess CU and other drugs use prospectively yearly from age 13 years across adolescence. Youth were assessed again at 23 years, and asked to report on substance use frequency, mental health, and the social environment. Assessments of CU quantity and potency, substance use problems and dependence symptoms were also collected. The main, indirect and moderating effects of individual, social and demographic factors have on the link between CU age of onset and later substance use and other problems is currently being examined using a variable-centred approach, in which regression and path analyses are conducted to examine the unique, or additive, effects of separate factors as predictors and moderators. A second person-centred approach such as Latent Class Analysis will also be used, which allows for an examination of an additive/interactive combination of factors.

FINDINGS
Data analysis is ongoing. However preliminary analyses will be presented at the November meetings.

IMPLICATIONS
As data analysis has yet to be completed, only potential implications are mentioned. This study has the potential to determine whether CU age of onset is a true risk factor and identify what early individual and environmental risk factors predict later substance use problems. It could also provide much needed empirical information about how individual and environmental factors interact to increase or mitigate the risk of developing substance use and other problems. This, in turn, would help identify a) who is more likely to develop substance use and other problems by early adulthood and b) relevant targets for prevention efforts (e.g., delaying age of onset or focusing on personal and environmental common or moderating factors), and better guide policy.
Developing cannabis education and harm reduction messages with youth

NOMINATED PRINCIPAL INVESTIGATOR(S)
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KEY MESSAGES
Most cannabis education utilizes a universal approach that conceptualizes all use by youth as equivalent. These programs and interventions focus on providing health information and facts about use, or on bolstering individual-level factors such as healthy decision-making, self-esteem and social skills. However, our youth-engaged research indicates that these approaches do not resonate with many youths because they neglect the culture and context (the how, when and why) that shapes use. Therefore, our research supports the development of youth-centred cannabis education grounded in harm reduction and young peoples’ lived experiences.

ISSUE
While there is high prevalence of cannabis use among Canadian youth, risk for potential harms and for problematic use of cannabis is not distributed equally, a function of health and social inequities. Legalization presents the opportunity to either mitigate or exacerbate the association between cannabis-associated harms and what is termed ‘structural marginalization,’ which results from intersecting determinants of health including socioeconomic status, racism, gender discrimination, trauma and social exclusion. Cannabis education developed specifically for youth whose structural contexts position them at greater risk for harms and problematic use is non-existent and is urgently needed.

AIM
The rationale for this project is that the experiences of youth most at risk for cannabis-associated harms are not accounted for in current prevention and education research or program development. As such, there is a pressing need to engage directly and meaningfully with structurally marginalized youth, so that cannabis education resonates with their lived experiences and the contexts that influence their substance use. The goal of our research is to generate evidence-informed and equity-oriented resources to reduce the potential for harms associated with cannabis use among Canadian youth who experience structural marginalization.

STUDY DESIGN
Informed by a harm reduction approach, our study uses qualitative methodology and arts-based research to develop education messages that are youth-centred and responsive to the structural contexts that influence youth cannabis use and the potential for harms. In qualitative interviews (n=50) in Calgary and Vancouver, we will explore the experiences of youth from marginalized contexts, how they view cannabis use, how they understand the potential for problematic use, and the approaches and messages about reducing cannabis harms that resonate with their lived experiences and contexts of use. Drawing from interview data, we will use digital storytelling and partner with youth (n=6) to co-create education messages about reducing cannabis harms, ‘by youth for youth.’ Use of this novel, arts-based knowledge mobilization strategy will support us to engage participants with lived experience and to disseminate our study findings.

FINDINGS
TBD

IMPLICATIONS
TBD
Effects of access to regulated cannabis on a vulnerable population

NOMINATED PRINCIPAL INVESTIGATOR(S)
William G. Honer, University of British Columbia

KEY MESSAGES
1) Cannabis use is one of multiple co-occurring risk factors for psychosis.
2) Risk increases in proportion to days per week of use.
3) The risks in the year prior to legalization, compared with the year after, did not differ.
4) Methods of accessing cannabis following legalization were little different from the year prior; regulated cannabis was not widely used.

ISSUE
Cannabis was legalized and regulated in Canada on October 17, 2018. Concern for possible adverse effects including an increase in people experiencing symptoms of psychosis resulted in support for several research initiatives. Of primary concern was a possible change in psychotic symptoms after cannabis legalization in a vulnerable group living in precarious housing or homelessness. In this group prior to legalization, cannabis use, and days per week using contributed to psychosis, additively with other risk factors including a past history of psychosis, being a man, concurrent methamphetamine and alcohol use, and recent experience of trauma (Jones AA et al., PLOS Medicine 2020;17:e1003172).

AIM
The broad objective was to collect evidence for beneficial, neutral, or adverse effects of legalization and regulation of cannabis on mental health and substance use in a vulnerable group.

STUDY DESIGN
Since 2009, we have followed over 500 participants living in precarious housing or homelessness, with about 50% experiencing psychotic disorders (Honer WG et al., Can J Psychiatry 2017;62:482-492). A subsample of 213 members of this cohort was asked about cannabis use; about half were current users, and about half of users reported consumption for “medicinal” reasons including anxiety, sleep problems, pain, and to stimulate appetite. Just under 10% of this group also endorsed feelings of paranoia related to cannabis use. We carried out an analysis of monthly cannabis use, and symptoms of psychosis in 318 members of the cohort, spanning one year prior to, and one year after cannabis legalization.

FINDINGS
The final analysis we carried out compared the proportion of cannabis users with psychotic symptoms for the 12 months proceeding, and 12 months subsequent to legalization. Days per week of cannabis use did not appear to be different – most users reported daily use. About half of users reported symptoms of psychosis prior to legalization; this was unchanged in the year after. Similarly, the severity of 5 key symptoms of psychosis (delusions, conceptual disorganization, hallucinations, suspiciousness and unusual thought content) assessed monthly was unchanged. These findings are perhaps not surprising, as access to government-approved, regulated cannabis was minimal, and non-regulated cannabis was available, at least during this first year following legalization.
IMPLICATIONS

Days per week of cannabis use is one of multiple factors contributing to psychosis in precariously housed or homeless persons. Delivery of health care services in this setting might benefit from an integrated practice model, oriented to complex, comorbid disorders including substance use, mental and physical illnesses. The implementation process for providing access to government regulated cannabis might benefit from consideration of neighbourhood characteristics, including the full range of non-prescribed substances available, and competing methods of providing access and marketing.
Investigating cannabis as harm reduction during a community-wide overdose crisis

NOMINATED PRINCIPAL INVESTIGATOR(S)
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KEY MESSAGES
As data collection and analysis has been delayed by COVID-19, findings are still being developed.

ISSUE
Marginalized people who use drugs (PWUD) continue to bear the heaviest burden of Canada’s ongoing overdose crisis; new interventions are urgently needed to lower their risk of overdose death. Preliminary ecological analyses have raised the possibility that cannabis might be a substitute for illicit opioids, especially among PWUD; also, community groups in some Canadian cities are distributing cannabis at no cost to PWUD at highest risk of overdose. However, therapeutic cannabis use among PWUD is not well understood, and its risk and possible benefits need to be better described, especially in the context of co-occurring mental health conditions.

AIM
We sought to better understand therapeutic cannabis use among PWUD by: implementing/validating a new psychometric tool to measure therapeutic and problematic cannabis use; collecting detailed data on cannabis use strategies (e.g., type, strains, dose) and access patterns; and assessing relationships between cannabis use and important drug-using outcomes (e.g., overdose) and mental health comorbidities (e.g., depression) among participants in three long-running community-recruited prospective cohorts of PWUD in Vancouver, BC.

STUDY DESIGN
We recruited individuals who reported recent (i.e., ≥ 1 time in the previous six months) cannabis use participating in one of three combined prospective cohorts of PWUD in Vancouver: the Vancouver Injection Drug User Study (VIDUS, HIV-negative adults who inject drugs); the AIDS Care Cohort to evaluate Exposure to Survival Services (ACCESS, HIV-positive adults who use drugs); and the At-Risk Youth Study (ARYS, street-involved people who use drugs younger than 28 years.) Individuals completed an interviewer-administered questionnaire including the Comprehensive Cannabis Assessment Tool, measurement of cannabis use patterns (e.g., frequency, amount, type/strain) and access points. Additional data to address aims, including measures of mental health comorbidities, was confidentially accessed from the parent cohorts.

FINDINGS
As a result of the COVID-19 pandemic and resulting safety precautions, in-person data collection was suspended in March. Delays in participant recruitment and data entry mean data collection and analysis is ongoing.
Chronic cannabis exposure in adolescent vervet monkeys

NOMINATED PRINCIPAL INVESTIGATOR(S)
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KEY MESSAGES
The project has been considerably delayed because of in big part the pandemic and with the difficulty with the Kittitian government to import the compound on the island.

ISSUE
We have encountered major difficulties in completing the project on time. The COVID-19 pandemic has been the major problem since confinement made it such that it was not possible to access the laboratory on the island of Saint Kitts (where the monkeys are). The island is closed since February 2020. The compound to be tested (cannabis) required a lot of paperwork from the local government.

AIM
Our main goal was to evaluate the pharmacokinetics of oral cannabis administration in adolescent vervet monkeys and gather preliminary data on the behavioural consequences of cannabis consumption.

STUDY DESIGN
The initial timeline was:
1) to obtain the Ethics Committee approval from both the Université de Montréal and the Behavioural Science Foundation of Saint Kitts
2) screen for cannabis preferring monkeys
3) initiate the pharmacokinetics experiments
4) proceed with the behavioural evaluation pre- and post-treatment.

FINDINGS
So far, we were able to obtain the Ethics Committee approvals, set up a complete behavioural laboratory with state-of-the art video camera system for measuring social behaviour in the treated monkeys, setting up the Object Retrieval Test apparatus and procedure. At this moment, our data gathering on the cannabis-treated monkeys has been plagued by the pandemic and the experiments have been halted. The pharmacokinetics experiments will be handled by the chief veterinarian in Saint Kitts once the new THC compound is delivered (94% purity), expected this month.

IMPLICATIONS
The repercussions of the study are enormous given that cannabis has been legalized by the Canadian government and consumption among the young has increased significantly. The brain completes its maturation by the age of 21 and is vulnerable to drugs during the whole adolescent period. A grant proposal based on this study will be submitted to CIHR for a five-year period.
Cannabis and workplace fatalities: Establishing a baseline in Ontario

NOMINATED PRINCIPAL INVESTIGATOR(S)
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KEY MESSAGES

1. Early indications suggest information on the event leading to a workplace fatality and results of toxicology assessments can be reliably extracted. However, using only coroner data to identify workplace fatalities may lead to missed cases.

2. Some key data elements in coroner records, including interpretation of toxicology results, signs of impairment, and eyewitness accounts, are not consistently documented. Type of toxicology testing conducted also appears to vary across cases.

3. Coroner records represent a useful source of information on factors associated with workplace fatalities, but their utility as a measure of surveillance for cannabis involvement in workplace fatalities is unclear.

ISSUE

Cannabis involvement in workplace injuries has been identified as an important surveillance indicator for evaluating the impact of legalization. However, there is no existing population-based data source that can readily be used to estimate and monitor the extent of cannabis involvement in workplace injuries in Canada. Coroner records, which provide detailed information on the causes and circumstances of death, may represent an important existing source of data for measuring trends in cannabis use involvement among fatally injured workers. However, the quality and extent of data on toxicology and impairment in coroner records is unclear.

AIM

The overall objective was to assess the feasibility of using coroner data as a data source for surveillance of cannabis-related workplace fatalities. Using coroner data from 2008 to 2018 in Ontario, the specific objectives were:

1. to measure the proportion of workplace fatalities that undergo toxicology testing, assess the nature and quality of toxicology data, examine the worker-, workplace-, and incident-related factors associated with testing, and describe trends over time

2. among cases with toxicology data, estimate the nature and extent of cannabis involvement in workplace fatalities, explore variation by worker-, workplace-, and incident-related factors, and describe trends over time.

STUDY DESIGN

The study was a retrospective, population-based descriptive study. The target population included all acute, unexpected, unintentional, non-natural deaths occurring in the course of employment from 2008 to 2018 in Ontario and investigated by a coroner. We consulted with our project advisory committee and reviewed a sample of coroner records to identify the key elements to be extracted from the records. A standardized database for data abstraction was developed. The coroner’s office initially provided a list of case numbers believed to be eligible based on date of death, manner of death, and primary environment of incident. The full set of files for each potentially eligible case were retrieved to confirm eligibility. All eligible cases were reviewed by two data abstractors and information was extracted on incident leading to the fatality, fatality information, post-mortem examination and toxicology, evidence of impairment, investigations conducted, work and workplace characteristics, sociodemographics, health and lifestyle.
FINDINGS
A total of 970 workplace fatalities were identified by the coroner’s office. To date, 100 cases have been reviewed (2014-2018), of which 68 were considered eligible (68%). Mean age was 47.5 and 94% were male. Most common work environments were construction sites (28%), commercial driving (16%), and farms (13%). A total of 79% had toxicology completed with variable testing methods. Of these, 12% had detectable cannabinoid levels. Only one case was interpreted as being potentially contributory. Observations of potential impairment-related behaviour were rarely provided. Data abstraction was on hold due to COVID-19. Further data abstraction to continue.

IMPLICATIONS
Coroner records represent a potentially rich source of data on the mechanisms leading to workplace fatalities, which may help to inform interventions to improve occupational safety. However, based on our preliminary impressions, the utility of coroner records to act as a source of surveillance data on cannabis-related impairment in workplace fatalities is uncertain. While they provide important information on toxicological findings that are not otherwise systematically collected, inference on whether cannabis use and impairment is a contributory factor based on toxicology is not straightforward and is rarely done by coroners.
A pilot study for prevention of cannabis-related harms among youth and young adults

NOMINATED PRINCIPAL INVESTIGATOR(S)

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KEY MESSAGES

Due to COVID-19 disruption on research at Dalhousie University, data collection had to be paused on this project and is resuming shortly; therefore, findings for the study are not yet available, precluding the production of key messages based on the grant. However, once data collection finalizes, a final report will be provided to CIHR summarizing key take-aways and messages from the project.

ISSUE

Researchers recognize that only a small portion of individuals with cannabis use problems ever seek treatment. Therefore, developing effective interventions is urgently required to meet the needs of people who already use cannabis, but who are not currently receiving specialty treatment for cannabis addiction. To date, the impact of providing an easily accessible intervention platform for cannabis problems has not been evaluated.

AIM

The Canadian Research Initiative on Substance Misuse (CRISM) is developing an online intervention platform (Screening, Self-Management and Referral to Treatment; SSMRT), accessible to the general public, and intended to provide online access to a suite of efficacious screening and intervention resources. The project will evaluate whether using the SSMRT program reduces problems associated with using cannabis. The goal is to answer the following research questions:

1) Will young adults who use the SSMRT platform experience greater cannabis problem reduction than those who do not use the self-help platform?

2) What factors predict reductions in cannabis problems for those who engage with SSMRT?

STUDY DESIGN

An online survey will be administered to a sample of 1,446 university students with 723 randomly selected respondents receiving an invitation and link to SSMRT in a two-group (SSMRT exposure versus no exposure) open-label pilot RCT. Sample size is based on the number of students who have previously provided baseline data during phase one of SSMRT development. The proposed research will extend the baseline design to administer follow-up surveys at 12 months and 18 months after the initial data collection, providing access to SSMRT to the treatment group at 12 months. Surveys will assess demographics, cannabis use problems (CUDIT; primary outcome variable), adherence to LRCUG, protective behavioural strategies for cannabis use (PBSM scale), interest in substance use supports, and personal well-being (PWI scale).

FINDINGS

Due to COVID-19 disruption on research at Dalhousie University, data collection had to be paused on this project and is resuming shortly; therefore, findings for the study are not yet available.

IMPLICATIONS

The SSMRT platform addresses significant gaps in unmet healthcare needs for current cannabis users. Results from the proposed pilot study will be used to inform the design of a subsequent multi-site RCT application to CIHR, by providing estimates of (a) rates of uptake for the intervention platform, (b) attrition in an 18-month follow-up, and (c) effect size for SSMRT. Should SSMRT prove to be helpful, it can be expanded as a nationally administered free resource that provides evidence-based support for all users of cannabis, regardless of whether they are having cannabis-related problems.
Cannabis for the prophylactic treatment of migraine: A randomized double-blind placebo-controlled clinical trial

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KEY MESSAGES
Migraine is a common and disabling neurological condition, resulting in recurrent attacks of headache and other neurological symptoms that can severely limit an individual’s day-to-day function. Worldwide, considering all medical conditions, migraine is the second leading cause of years lived with disability. Currently, there is no cure, but migraine disability can be reduced for some patients with various therapies. However, each of these has its own set of limitations and side effects and many patients do not benefit from these therapies, leading to a need for new types of treatments. Preliminary data and pathophysiological mechanisms show the potential for cannabis use in migraine, making it a good candidate to study in this condition.

ISSUE
To date, there are no published placebo-controlled clinical trials of cannabis for the treatment of headache disorders, including migraine. The data that exists consists of retrospective case series, observational studies, and only one small clinical trial that compared cannabis to Amitriptyline, an established migraine preventative agent. Yet, cannabis use has become increasingly popular in the last one to two years for migraine patients, as current medications are not adequate to meet the needs of these patients. This is in fact an enormous area of unmet need, especially as migraine is common, disabling, and affects individuals in their most productive years of life, where family and work demands are at their highest. Therefore, there is an urgent need to study cannabis for this condition in a proper randomized placebo-controlled trial.

AIM
The study has not yet been conducted due to circumstances mentioned below. The study is a phase II randomized, double-blind, placebo-controlled clinical trial to evaluate the efficacy and safety of a high concentration cannabidiol soft gel capsule compared to placebo as a preventative therapy for adult patients with chronic migraine. The primary endpoint of this study will assess the mean change in the number of headache days between the four-week baseline period compared to the four-week period just preceding the three-month follow-up visit. Secondary endpoints will look at headache intensity, responder rates, measures of disability, quality of life, anxiety, depression, and sleep at various time points. Safety will be monitored by adverse events, clinical assessments, laboratory and ECG assessments, and a data safety monitoring board.

STUDY DESIGN
The study design is a randomized, double-blind, placebo-controlled clinical trial, with three arms: placebo, lower dose CBD (50 mg BID), and higher dose CBD (100 mg BID). The rationale for these doses comes from a small European study which assessed chronic migraine patients taking Cannabis versus Amitriptyline. The study duration is 28 weeks with four visits to the study centre and two telephone visits. The 28 weeks includes a baseline period of data collection for four weeks, randomization into one of the study arms with 12 weeks of therapy, followed by another 12 weeks of monitoring, and a final visit at 28 weeks. The study will include 120 male and female participants aged 25 and over with a diagnosis of chronic migraine based on ICHD-3 criteria (International Classification of Headache Disorders, version 3.0). In this study, we have decided to study a CBD-predominant soft gel capsule, because in addition to its anti-nociceptive properties, CBD is free of psychoactive effects. Thus, it will permit patients to function throughout the day. The lack of psychoactive effects also improves the blinding process.
FINDINGS
Unfortunately, we have not yet been able to start this study due to a Health Canada policy change that came into effect shortly after we submitted our Clinical Trial Application (CTA) to Health Canada for review. This policy change indicates that cannabis products that are to be studied in a clinical trial must have extensive pre-clinical studies performed on them prior to submitting a CTA to Health Canada (i.e., cannabis is viewed similar to any other drug that is to undergo a clinical trial, despite multiple cannabis products being sold commercially and used by patients and the general public). I have tried since that time to find an industry partner to work with that would have pre-clinical studies completed on their particular cannabis strain but have not been successful. Only GW pharmaceuticals have conducted preclinical work on their drug, Epidiolex, but declined to collaborate.

IMPLICATIONS
Although this study has not been initiated, I do hope to find a partner to work with that meets Health Canada requirements. Our hypothesis is that subjects receiving active drug will have a greater reduction in their frequency of headache days between the 12-week visit and baseline, as compared to subjects receiving placebo. A reduction in headache frequency means a reduction in disability and improved functioning and quality of life. This then translates to a reduced burden of disease for the patient, their family, and for society, as migraine has a huge socioeconomic impact. In addition, this study has the potential to shed light on which strain, formulation, and dosage of cannabis may be beneficial in migraine. Currently, patients use a wide variety of strains, formulations, and dosing, without knowing what may benefit them.
Examining the pharmacological and non-pharmacological influences of cannabidiol (CBD) on stress responsivity in healthy men and women

NOMINATED PRINCIPAL INVESTIGATOR(S)
Sean Barrett, Dalhousie University

KEY MESSAGES
Cannabidiol (CBD) related placebo effects produce subjective drug-like responses, as well as diminish anxiety related responses, particularly among those who believe CBD.

ISSUE
To understand the mechanisms through which CBD impacts acute stress and anxiety in healthy adults.

AIM
To determine the extent to which CBD effects on stress and anxiety related responses can be attributed to placebo response.

STUDY DESIGN
Double-blind, cross-over experiment

FINDINGS
CBD expectancy impacts several subjective and physiological responses.

IMPLICATIONS
Studies that examine CBD related effects in humans need to account for the contributions of expectancy in producing observed drug responses.
The effect of cannabidiol vs. placebo on persistent post-surgical pain following total knee arthroplasty: A multicentre, randomized pilot trial

NOMINATED PRINCIPAL INVESTIGATOR(S)

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KEY MESSAGES

Regulatory hurdles associated with acquiring approval from Health Canada to launch clinical trials of medical cannabis have proven extremely difficult to meet. We have now met with dozens of licenced producers that provide medical cannabidiol (which is non-psychotropic) to Canadians and engaged in detailed discussions with nine to identify a cannabidiol product that meets Health Canada’s requirements for GMP-certification. So far, we have been unsuccessful in identifying a suitable product to begin our pilot trial.

ISSUE

In 2017-2018, more than 70,000 total knee replacements were performed in Canada; however, 27% of patients report persistent pain after surgery. Chronic pain after surgery is often managed with opioid therapy, which is associated with rare but serious adverse events, such as overdose and death. Several studies have found that greater pain just before and after knee replacement surgery is associated with the development of chronic pain, suggesting that reducing peri-operative pain may help prevent persistent post-surgical pain. We proposed to explore the role of cannabidiol for the prevention of persistent pain after total knee replacement.

AIM

The primary objective of our pilot trial was to assess the feasibility of a definitive trial to determine the effect of medicinal cannabidiol, versus placebo, on the proportion of patients experiencing persistent pain following total knee replacement surgery. The primary objective of the definitive trial is to determine if medicinal cannabis add-on therapy, versus placebo, reduces the proportion of patients experiencing persistent post-surgical pain at six months following knee replacement surgery.

STUDY DESIGN

The pilot trial is a parallel design randomized controlled trial of 40 patients scheduled to undergo knee replacement surgery. Eligible patients will be randomized, 1:1, to one of two treatment arms:

(1) cannabinoid oil plus standard treatment, or
(2) placebo plus standard treatment. Health care providers (surgeons, anesthesiologists, nurses), patients, outcome assessors, and data analysts will be blinded to treatment allocation. Participants will be followed for six months after surgery.

FINDINGS

Despite widespread sale and use of cannabidiol by Canadians for medical purposes, we have been unable to identify a product that Health Canada will approve for use in a clinical trial. We have previously entered detailed discussions with CannTrust, Green Organic Dutchman, TerrAscend, Canopy Growth Company, Cronos Group Inc, Tilray, Aurora, Aphria Inc, and Folium Biosciences, but have not been able to identify a suitable cannabidiol product. We are currently working with MediPharm Labs and hope to identify a GMP-compliant cannabidiol product to launch our pilot trial.
IMPLICATIONS

We have registered our protocol in clinicaltrials.gov (NCT03825965) on Feb. 20, 2019, and acquired ethics approval from the Hamilton Integrated Research Ethics Board (HiREB) on April 8, 2019. Despite considerable efforts, our study has not been able to initiate due to difficulty in meeting Health Canada requirements. Our experiences highlight that clinical trials of medical cannabis may not be feasible in Canada.
Cannabidiol as a potential therapeutic target for mild traumatic brain injury recovery in female rats

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KEY MESSAGES
Women experience more, and more severe, symptoms than men following a mild traumatic brain injury, with the greatest divergence in psychiatric symptoms (anxiety and depression) and pain. Studies show that the menstrual cycle stage at the time of the accident affects the impacts of a traumatic brain injury (TBI) — the luteal phase is associated with more, and more severe, symptoms. This phase is characterized by a heightened inflammatory response, which can be reduced by a dose of cannabidiol, an extract derived from cannabis. Our project aims to measure the therapeutic potential of cannabidiol to reduce post-TBI symptoms by suppressing cerebrovascular inflammation mechanisms.

ISSUE
Solutions are urgently required to reduce the development of symptoms and their persistence in women with mild traumatic brain injuries, given the resulting psychological suffering and the heightened risk of relapse of depressive or anxious episodes for the rest of their lives.

AIM
To evaluate the therapeutic potential of cannabidiol to reduce symptoms following a mild traumatic brain injury through its anti-inflammatory properties.

STUDY DESIGN
The study design involves three independent variables: sex (female rats with TBIs during the luteal phase; male rats) X injury (TBI vs. no TBI) X treatment (CBD vs. placebo). In the female rats, the TBI will be induced at the moment of the peak level of progesterone in their menstrual cycles. The variables in neurological outcome include a quantification and precise spatial resolution of cerebrovascular inflammation and diffusion measures using a 7-Tesla MRI. The behavioural outcomes include anxiety, memory, motor functions and direction tests in a maze.

FINDINGS
Project nearing completion (six-month interruption caused by the pandemic in Montreal). Project completion is forecast for early November (assuming that the labs will not be closed again by public health, as Montreal is back in a state of health crisis as of September 28, 2020).

IMPLICATIONS
This study could show, thanks to an animal model controlling for a set of confounding variables, that cannabidiol is effective in reducing symptoms following a traumatic brain injury, and in a more significant way in women. This animal validation step is essential before being able to propose a clinical trial in humans to study the therapeutic potential of cannabidiol to counter symptoms following a TBI.
Health outcomes of medical cannabis authorization in adult patients from Alberta and Ontario, Canada

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KEY MESSAGES
This study presents Canada’s largest and longest (to date) followed cohort of medically authorized cannabis patients in Alberta and Ontario. Notably, our study contributes new unprecedented insight into the demographics of this medically authorized cannabis adult population, and their health outcomes in anxiety, depression, and chronic opioid use.

ISSUE
Legalization of medical cannabis around the world has created excitement among both patients, clinicians and researchers as to the impact that the therapy will have on patients. However, evidence on patient outcomes is limited and where it does exist, it is often of low quality. Many patients and clinicians are interested in the use of cannabis for treating mental health disorders (e.g., anxiety and depression) and its potential effect on opioid medication use.

AIM
There is an urgent need to build the knowledge base given increasing access to legal cannabis in the United States and Canada. To address this gap, our study constructs Canada’s largest and longest followed cohort of patients authorized for medical cannabis use ever established (>80,000 patients). This study addresses a major evidence gap and clarifies the health outcomes of currently authorized medical users — including outcomes in anxiety, depression, opioid use and characterization of medical cannabis adult population.

STUDY DESIGN
This included several cohort studies of patients in Alberta and Ontario, Canada, who were authorized medical cannabis. The GAD-7 and PHQ-9 cohort studies were between 2014-2019 in both Alberta and Ontario; whereas the opioids study was a matched controlled interrupted time series analyses between 2013-2018 in Alberta, Canada. The study population consisted of all adult patients authorized to access medical cannabis attending a chain of specialized clinics in the provinces of Alberta and Ontario, Canada, and all authorized medical cannabis in Alberta using chronic opioids. Participants were adults of any sex, ethnicity and socioeconomic status who were seeking medical cannabis.

FINDINGS
For both GAD-7 and PHQ-9, the study found no evidence of a therapeutic benefit associated to authorizing medical cannabis for patients seeking help with anxiety, depression, and disorders related to both, however, future well-controlled clinical trials are needed in order to fully examine risks or benefits associated with using medical cannabis to treat mental health conditions. For opioid use, our study found that medical cannabis authorization showed differential effects on opioid utilization, which was dependent on initial opioid dose. The greatest clinical benefits appear to be in those patients who were on a high dosage of opioids (OME>100).

IMPLICATIONS
The GAD-7 and PHQ-9 study provides an important bridge for some of these knowledge gaps regarding cannabis and mental health outcomes. These findings help contribute to the knowledge base on current and potential population health impacts of cannabis use, while at the same time, providing future direction to the field of mental health around cannabis research. Likewise, our opioid study is critical in building and informing evidence on how medical cannabis can have downstream influences in both opioid drug abuse prevention and pain treatment needs in clinical practice.
A proof-of-concept, double-blind, randomized, placebo-controlled trial evaluating the efficacy and safety of cannabis-infused MCT oil for treatment of insomnia in major depression

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KEY MESSAGES

Co-morbid chronic insomnia persists in 20% of individuals with major depression and is associated with worse illness course, worse response to treatment and higher risk of suicide behaviour and relapse. Thus, using a rigorous randomized, placebo-controlled clinical trial, the present proposal is a first step toward a better understanding about the potential benefits and harms of the use of cannabinoids for treatment of chronic insomnia in individuals with major depression.

ISSUE

Sleep disorders were among the top three most common reasons why physicians prescribed medicinal cannabis, but efficacy and safety data from placebo-controlled trials are lacking.

AIM

To conduct a pilot, randomized, placebo-controlled clinical trial, to investigate the use of cannabis-infused oil for treatment of comorbid insomnia in individuals with major depression.

STUDY DESIGN

A pilot, three-arm, randomized, double-blind, placebo-controlled trial.

FINDINGS

This study is waiting Health Canada approval.

IMPLICATIONS

This project has the potential to directly impact patient care by providing evidence for or against the use of cannabis oil in the treatment of insomnia in individuals with depression. In addition, the results from this clinical trial will inform the health care system more broadly about prescription and accessibility (or concerns) of the use of cannabinoids for depressed subjects with insomnia.
Medical cannabis against chronic musculoskeletal pain — a mixed methods study to describe use and to identify its facilitators and barriers among Canadian patients and doctors

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KEY MESSAGES
Chronic musculoskeletal pain still causes important suffering in many patients, which is unsatisfactorily relieved by current treatments. Some patients explore medical cannabis together with their physicians. Both doctors and patients are easily lost in this endeavor, due to lack of evidence on MC effectiveness and safety, as well as to the diversity of ways to prescribe and procure medical cannabis, somewhat complicated by the recent legalization of recreational cannabis in Canada. Preliminary results show a large array of barriers and facilitators for the use of MC against CMP among patients and physicians, so that tailored information for both groups is needed. The last part of the study will quantify these barriers and facilitators so that tailored information can be produced, as needed for shared decision making on MC against CMP.

ISSUE
Effective therapeutic options for relieving chronic musculoskeletal pain (CMP) are limited, and treatment remains suboptimal for many patients: f. e. only one third of patients treated with a gabapentinoid will benefit from it by a pain relief of at least 50%. Clinicians find management of CMP difficult and still advocate long-term treatment with opioids, although their effectiveness is highly uncertain, dramatic adverse effects are common, and opioids have recently become a major public health problem. The opioid crisis reached all Canadian provinces, making it urgent to explore new options to treat CMP. Patients and physicians consider medical cannabis (MC) as a possible analgesic option although its effectiveness and safety remain controversial and treatment modalities unknown: both patients and physicians lack crucial treatment information.

AIM
This study focussed on the use of MC against CMP among adults and aimed at:
1. describing the use of MC in Québec and Canada, and the main characteristics of users and prescribers
2. identifying the therapeutic and adverse effects of MC from the users’ perspective
3a. identifying the psychosocial, organizational, socio-demographic and health-related factors that influence the use and prescription of MC and
3b. quantifying the impacts of these factors on the use and prescription of MC in the management of CMP.

STUDY DESIGN
The study used mixed methods to collect data from patients affected by CMP and their physicians. The qualitative phase identified obstacles and facilitators for the use AND for the prescribing of MC against CMP in patients suffering from CMP and in physicians. Reasoned samples of patients and physicians were recruited and information was collected by semi-structured interviews. For the quantitative phase, a pan-Canadian survey will be conducted, with a questionnaire being built from the results of the qualitative phase. We also intend to analyze data on the users and prescribers of MC from the Registre Cannabis Québec (RCQ).
FINDINGS
The study is ongoing, because the COVID-19 pandemic delayed analyses on RCQ data as well as qualitative analyses. However, using the Theory of Planned Behaviour, a large array of facilitators and barriers regarding the use of MC to treat CMP has been identified and related to perceptions and past experiences, environmental influences, perceived advantages and disadvantages or barriers, as well as health system factors. Over 35 interviews with both patients and physicians documented both the urgency to improve treatment of CMP and the need for comprehensive, high-quality, updated information on effectiveness, safety and all available prescribing, procurement and treatment options.

IMPLICATIONS
The most important preliminary finding is the need expressed by patients and physicians for improved information and for better treatment follow-up, particularly by physicians. These preliminary findings motivated us to presently develop a follow-up project aimed at improved shared decision-making between CMP patients and their physicians, regarding the use of MC. Decision boxes for patients and physicians and an online-based information and training program will both be developed: pilot funding is being sought and once information tools are developed, a CIHR grant will be submitted.
Assessing the potential for using cannabidiol as a management option for anxiety in Alzheimer-dementia patients

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KEY MESSAGES
Alzheimer disease; neuropsychiatric symptoms; anxiety; aggression; cannabidiol; long-term care

ISSUE
Behavioural and psychological symptoms of dementia (BPSD) can be as high as 95% in Alzheimer’s Disease (AD) patients. The most common BPSD is anxiety, but other symptoms include aggression, depression, and hallucinations. Current treatments rely on antipsychotic medications, which have concerning adverse-effect profiles. The search for a more effective and therapeutic alternative to control BPSD in AD patients has recently focused on cannabis plant extracts. However, the lack of evidence-based information on safety, tolerability, and general effectiveness of such cannabinoids has promoted reluctance amongst physicians to authorize cannabis or related extracts for the management of BPSD in AD.

AIM
Our long-term objective is to determine the safety and tolerability of cannabidiol (CBD), a cannabinoid with effects on the brain, but lacking the ‘high’ associated with the cannabinoid delta-9-tetrahydrocannabinol (THC), in clinical populations. We will examine the role for CBD in managing the symptoms of anxiety and agitation in individuals with AD. As the population continues to age, the need to improve quality of life and independence is becoming increasingly essential. Thus, any benefit of CBD to the patient — and to their caregivers — is important, not only to those directly involved, but ultimately to our increasingly burdened health care system.

STUDY DESIGN
The proposed project begins with (1) an in vitro-in vivo extrapolation of cannabinoid (CBD & THC) permeation and metabolic stability (using Caco-2 polarized epithelial cell cultures) to facilitate oral dose determination. This will inform on (2) a pharmacokinetic study of a single-dose, open-label, high-dose CBD to THC plant extract (in olive oil) in healthy adults to validate the in vitro-in vivo extrapolation process; and will support (3) an open-label, add-on, pilot study of the efficacy of the plant extract (in olive oil) for managing BPSD and anxiety in an AD patient cohort (while monitoring for safety and tolerability). Our individual areas of expertise and experience with a recent similar protocol investigating the safety and efficacy of CBD in children with refractory epileptic encephalopathy guarantees the project’s completion within the projected timeframe.

FINDINGS
The study has yet to begin. Although we have applied to Health Canada for a license to hold/dispense cannabis extracts, we have yet to hear back from them. The University of Saskatchewan is also trying to obtain an institutional license to cover future cannabis-related research.

IMPLICATIONS
Establishing a role for cannabidiol in the management of neuropsychiatric symptoms (e.g., aggression, etc.) in long-term care patients would be an alternative to present practice, which relies quite heavily on antipsychotic medications.
Managed alcohol programs and cannabis substitution: Feasibility and pilot study

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KEY MESSAGES
While Managed Alcohol Programs reduce many acute and social harms for those with severe alcohol use disorder (AUD), cannabis substitution programs (CSPs) are a potential therapeutic option to reduce chronic harms of long-term heavy alcohol consumption. This study explored the feasibility of implementation and potential research designs for evaluation of a CSP in MAP with six program sites. Recommendations included the development of a clinical intervention by programs with tailored cannabis dosing partially substituting for alcohol provision, with enhanced staffing, education, peer, and counselling supports. Practical and ethical concerns limit the possibility of conducting a controlled clinical trial and a within-subject control evaluation design with research funding for clinical staff support in a MAP-led CSP is recommended.

ISSUE
While there is robust evidence for strategies to reduce harms of illicit drug use, much less research attention has been paid to harm reduction strategies for people experiencing severe alcohol use disorder, homelessness, and street-based illicit drinking. Managed Alcohol Programs (MAPs) have developed in Canada as harm reduction options that provide safer sources and setting for drinking, housing, health, social and cultural supports. Stemming from findings from the Canadian Managed Alcohol Program Study (CMAPS) and preliminary literature on the role of cannabis in reducing alcohol consumption and related harms at the population level, cannabis substitution has emerged as a potential therapeutic tool in MAPs that may reduce the ongoing and unintended impacts of chronic and heavy long-term alcohol use among participants.

AIM
The aim of this study was to (1) explore the feasibility of the implementation and evaluation cannabis substitution programs in MAPs and to (2) develop a draft protocol for conducting a pilot study. Informed by the Consolidated Framework for Implementation Research (CFIR), we examined the characteristics, suitability and acceptability of cannabis substitution from the perspective of MAP decision makers, staff, and program clients and explored practical, legal, financial and ethical issues related to cannabis substitution.

STUDY DESIGN
We conducted surveys with seven decision makers, 17 staff and 19 clients at 6 different MAP sites across Canada. We interviewed organizational leaders about their support for the program and to receive approval in principle for the concept of cannabis substitution. This was followed by interviews with program staff and clients about their perceptions of the feasibility of doing cannabis substitution as well as the design and evaluation of the intervention. Further, we conducted a review of key ethical and legal considerations for cannabis procurement and evaluation with key stakeholders. Descriptive data along with learnings from the ethical and legal reviews were presented to program sites for feedback to inform the development of a draft pilot protocol.
**FINDINGS**

All program sites supported CSPs in principle. Based on the findings, the most feasible approach to CSP intervention is a partial substitution model implemented by MAP programs. This model would include a reduced number of doses of alcohol at specific administration times with dosing tailored to each participant. Dried cannabis was preferred by most participants, followed by capsule and edible forms of cannabis. Practical and ethical concerns related to procuring and managing cannabis within distributed sites limit the ability to pursue a clinical trial. However, MAPs would need to address issues related to funding and sourcing of cannabis prior to implementation. Further, requirements for program implementation include staff and agency education, additional financial resources and enhanced staffing, peer, social, and counselling supports for participants.

**IMPLICATIONS**

Key findings from this study suggest that cannabis substitution programs in MAPs are feasible and should proceed to pilot testing. The CSP intervention should be program-led with MAP programs sourcing and funding the cannabis as the most viable model within the current cannabis legislation. Program development should take into consideration the cultural and practical context of MAP with funding for additional clinical program staff and supports. Staff and agency education re cannabis and the intervention are important for successful implementation. Recommendations for a pilot study include the use of a “within-subject control” (i.e., pre and post-cannabis) evaluation design to avoid practical and ethical concerns and reduce potential harms to participants.