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CANNABIS USE TO MANAGE OPIOID CRAVINGS AMONG PEOPLE WHO USE UNREGULATED OPIOIDS DURING A DRUG TOXICITY CRISIS

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Abstract

Background—Accumulating evidence has indicated that cannabis substitution is often used as a harm reduction strategy among people who use unregulated opioids (PWUO) and people living with chronic pain. We sought to investigate the association between cannabis use to manage opioid cravings and self-reported changes in opioid use among structurally marginalized PWUO.

Methods—The data were collected from a cross-sectional questionnaire administered to PWUO in Vancouver, Canada. Binary logistic regression was used to analyze the association between cannabis use to manage opioid cravings and self-reported changes in unregulated opioid use.

Results—A total of 205 people who use cannabis and opioids were enrolled in the present study from December 2019 to November 2021. Cannabis use to manage opioid cravings was reported

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Ethics approval

The authors declare that they have obtained ethics approval from an appropriately constituted ethics committee/institutional review board where the research entailed animal or human participation.

University of British Columbia/Providence Healthcare research ethics board (H05-50233-A094)

CRediT authorship contribution statement

Hudson Reddon: Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Stephanie Lake:** Writing – review & editing, Funding acquisition. **Maria Eugenia Socias:** Writing – review & editing. **Kanna Hayashi:** Writing – review & editing, Project administration, Funding acquisition. **Kora DeBeck:** . **Zach Walsh:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Conceptualization. **M-J Milloy:** Writing – review & editing, Supervision, Project administration, Methodology, Funding acquisition, Conceptualization.

Appendix. Supplementary Table 1

by 118 (57.6%) participants. In the multivariable analysis, cannabis use to manage opioid cravings (adjusted Odds Ratio [aOR] = 2.13, 95% confidence interval [CI]: 1.07, 4.27) was significantly associated with self-reported reductions in opioid use. In the sub-analyses of pain, cannabis use to manage opioid cravings was only associated with self-assessed reductions in opioid use among people living with moderate to severe pain (aOR = 4.44, 95% CI: 1.52, 12.97). In the sub-analyses of males and females, cannabis use to manage opioid cravings was only associated with self-assessed reductions in opioid use among females (aOR = 8.19, 95% CI: 1.20, 55.81).

Conclusions—These findings indicate that cannabis use to manage opioid cravings is a prevalent motivation for cannabis use among PWUO and is associated with self-assessed reductions in opioid use during periods of cannabis use. Increasing the accessibility of cannabis products for therapeutic use may be a useful supplementary strategy to mitigate exposure to unregulated opioids and associated harm during the ongoing drug toxicity crisis.

Keywords

Cannabis; Opioids; Substitution; People who use drugs; Cravings

INTRODUCTION

Canada and many other jurisdictions are contending with the increasing harm associated with the drug toxicity crisis caused by the contamination of the illicit drug supply with fentanyl and other high-potency synthetic opioids (British Columbia Coroners Service, 2022; Public Health Agency of Canada, 2022). Overdose is now the leading cause of accidental death in Canada and the United States (Fischer, 2023), and the number of opioid toxicity deaths in the province of British Columbia reached an average of 6.4 per day during 2022 (42.2 per 100,000) (Public Health Agency of Canada, 2022). Concurrently, access to and use of cannabis has evolved following the legalization of cannabis cultivation, possession, acquisition and consumption for recreational purposes in 2018 (Bill C-45, 2018; Fischer, Lee, O'Keefe-Markman, & Hall, 2020; Fischer, Lee, Robinson, & Hall, 2021). The intersection of cannabis policy reforms with the opioid overdose epidemic have sparked public and scientific interest into the potential effects of cannabis use on the progression to using higher-risk substances such as prescription and unregulated opioids (Kvamme, Pedersen, Romer Thomsen, & Thylstrup, 2021; Nkansah-Amankra, 2020; Okusanya et al., 2020; Wilson et al., 2022).

There is accumulating evidence indicating that access to recreational and medical cannabis may have positive impacts on public health as a result of substitution effects, particularly among people who use opioids and stimulants (Lake, Walsh, et al., 2019; Lucas, 2017; Reiman, Welty, & Solomon, 2017). Substitution of prescription drugs is now the most common motive for cannabis substitution among medical cannabis users (Lau et al., 2015; Lucas, Baron, & Jikomes, 2019; Lucas et al., 2016) and state-level data identified that the introduction of medical and recreational cannabis laws in the United States were associated with decreases in opioid prescriptions (Bradford, Bradford, Abraham, & Bagwell Adams, 2018; Wen & Hockenberry, 2018), fewer opioid-related hospitalizations and lower rates of opioid overdose (Bachhuber, Saloner, Cunningham, & Barry, 2014; Livingston, Barnett, Delcher, & Wagenaar, 2017; Lucas, 2017; Vyas, LeBaron, & Gilson, 2018). Throughout the

drug toxicity crisis in Vancouver, Canada, analyses of prospective cohort studies found that nearly half of people who use unregulated drugs (PWUD) reported harm reduction uses for cannabis such as opioid substitution (Mok et al., 2021), and, in this population, cannabis use has been associated with reductions in opioid use, as well as injection drug use (Lake, Walsh, et al., 2019; Reddon et al., 2018; Reddon et al., 2020; Socias et al., 2021). However, other evidence from cohort studies and meta-analyses of general population samples have shown contradictory effects whereby cannabis use has been linked to increases in opioid initiation, opioid use disorder and overdose mortality, primarily among samples from the general population (Fergusson, Boden, & Horwood, 2015; Olfson, Wall, Liu, & Blanco, 2018; Wilson et al., 2022). The initial decreases in opioid overdose mortality associated with medical cannabis laws from state-level data in the United States have been found to reverse over time and states with medical cannabis laws experienced a 23% increase in opioid overdose mortality from 2010–2017 (Shover, Davis, Gordon, & Humphreys, 2019). As a result, there is uncertainty surrounding the potential harms and benefits of cannabis access and use during the drug toxicity crisis and experts have called for additional individual-level studies that directly measure cannabis use intentions (e.g., recreation, substitution) among populations uniquely vulnerable to cannabis- and opioid-related harm, and during a period of expanded cannabis market maturity (Myran, Imtiaz, Konikoff, Douglas, & Elton-Marshall, 2022; Tormohlen et al., 2021).

Despite this evidence gap, we are not aware of any studies that have specifically investigated the outcomes of intentional cannabis use to manage opioid cravings among PWUD. Existing studies have primarily analyzed regulatory changes at an ecological level, crude measures of cannabis use and retrospective motives for cannabis use (Bachhuber et al., 2014; Livingston et al., 2017; Lucas, 2017; Shover et al., 2019). Given the increasing harm of the drug toxicity crisis and ongoing maturation of the regulated cannabis market in Canada, evaluating how cannabis use patterns, such as substitution, impact opioid use behaviours will be important to inform public health and policy responses to mitigate the harms of opioid use and evolving cannabis access. In response, we sought to analyze the association between cannabis use to manage opioid cravings and the use of unregulated opioids among a structurally-marginalized population of PWUD in Vancouver, a setting with a high prevalence of cannabis use and the highest age-adjusted opioid mortality rate in Canada (*Canadian Cannabis Survey*, 2021; *Public Health Agency of Canada*, 2022). Given that several studies and meta-analyses have documented significant associations between cannabis use and opioid use among people living with chronic pain (Lake, Walsh, et al., 2019; Lucas, Boyd, Milloy, & Walsh, 2021; Okusanya et al., 2020), we conducted a sub-analysis to identify if the effects of using cannabis to manage opioid cravings on opioid use vary among people living with pain. We also conducted gender-stratified sub-analysis based on documented gender differences in cannabis use behaviours (e.g., frequency and quantity of use), harms (e.g., prevalence of cannabis use disorder) and treatment-seeking behaviours (Imtiaz et al., 2016; Khan et al., 2013).

MATERIALS AND METHODS

Data sources and participants

The data for this study was obtained from three open prospective cohort studies of PWUD in Vancouver, BC, Canada: AIDS Care Cohort to Evaluate Access to Survival Services (ACCESS); Vancouver Injection Drug Users Study (VIDUS), and At-Risk Youth Study (ARYS). Details of the cohort eligibility criteria and protocols have been described previously (Strathdee et al., 1998; Wood, Stoltz, Montaner, & Kerr, 2006). Briefly, participants from all three cohorts provided written informed consent, self-reported using unregulated/illicit drugs in the previous month (excluding or in addition to cannabis), and lived in the greater Vancouver area at the time of enrolment. VIDUS includes people who inject drugs (PWID), aged 18 years or older and tested seronegative for HIV at the time of enrollment. ACCESS includes PWUD (aged 18 years or older) who are living with HIV and VIDUS participants that seroconvert to HIV-positive. ARYS includes a younger group of PWUD (aged between 14–26 years old at study enrolment) who are street-involved, defined as having unstable housing or using street-based youth services (Debeck et al., 2013). Participants were recruited from the Downtown Eastside and Downtown South neighbourhoods of Vancouver, Canada through extensive street outreach and self-referral. These neighbourhoods experience high rates of substance use including cannabis and opioids, and recently community-led cannabis distribution programs have emerged in this setting to facilitate cannabis substitution among marginalized communities during the drug toxicity crisis (Strathdee et al., 1998; Valleriani et al., 2020).

At baseline and semi-annually thereafter, participants complete an interviewer-administered questionnaire that collected data including sociodemographic information, substance use patterns, HIV risk behaviors, and engagement with health and social services. The recruitment and data collection procedures from the VIDUS, ACCESS and ARYS study have been harmonized to facilitate pooled analyses. From December 2019 to November 2021, participants from these three cohorts who reported any form of cannabis use in the last six months were invited to complete a supplementary cannabis questionnaire in addition to their routine study follow-up. This questionnaire was completed once by each agreeing participant and collected data including frequency of cannabis use, route of administration, cannabinoid ratio (high THC vs. high CBD), cannabis source, motive for use (e.g., recreation, pain relief, substitution, self-medication) and effects of cannabis use on other substance use (e.g., substitution vs. complimentary effects). Participants are remunerated CA $40 for their time at each study visit for the parent cohorts and received an additional CA $40 if they completed the supplementary cannabis questionnaire. Between March 2020 and July 2020, all in-person data collection was suspended due to the COVID-19 pandemic. Once public health measures were implemented in July 2020, data collection was able to resume by completing participant interviews via telephone or videoconferencing. Study provided cell phones and private spaces were available to the participants if needed. Honoraria was provided as cash or e-transfer if participants had access to a bank account. All study procedures were conducted in accordance with the Declaration of Helsinki and written informed consent was been obtained from all participants. The study protocol has

been reviewed and approved by the University of British Columbia/Providence Healthcare research ethics board on an annual basis.

Study variables

The analytical sample for the present study included all VIDUS, ACCESS and ARYS participants who were aged 18 years or older, completed the supplementary cannabis questionnaire and reported opioid use in the last six months. The outcome of interest was self-reported reductions in opioid use during periods of cannabis use. This variable was operationalized by classifying participants as "1" if they responded "Somewhat agree" or "Strongly agree" to the item, "When I use cannabis, I don't need to use as much of the opioids that I am taking." Participants were coded as "0" if they responded "Strongly disagree," "Somewhat disagree" or "Neither agree nor disagree" to this item. The primary explanatory variable of interest was self-report of using cannabis to manage opioid cravings based on the item, "In the last 6 months, have you used cannabis to help reduce cravings for illicit opioids?" Based on previous studies analyzing cannabis substitution for opioid use, we selected secondary covariates hypothesized as potential confounders that were available in the VIDUS, ACCESS and ARYS cohorts (Kvamme et al., 2021; Lake, Walsh, et al., 2019; Lucas et al., 2019; Reiman et al., 2017). These variables were self-reported gender (male vs female); age (per five years older); race/ethnicity (white vs Black, Indigenous and people of colour [BIPOC]); licit employment (i.e., having a regular, temporary, or self-employed work vs none); residing in the Downtown Eastside (DTES) neighborhood of Vancouver (yes vs. no); access to free cannabis distribution programs (yes vs. no); homelessness (defined as living on the street with no fixed address at any time in the 6-month period preceding the follow-up interview); pain (Euroqol EQ-5D moderate-extreme pain, yes vs. no); cannabis use frequency (≥daily vs. <daily); high-THC cannabinoid ratio (high-THC vs. one-to-one), high-CBD cannabinoid ratio (high CBD vs. one-to-one). Gender categories were restricted to male and female since other categories included counts too low to produce stable effect estimates (Serdar, Cihan, Yucel, & Serdar, 2021). The Euroqol EQ-5D health utility instrument has been shown to be a valid and reliable instrument for assessing chronic health states among people living with pain and PWUD (Obradovic, Lal, & Liedgens, 2013; van der Zanden et al., 2006). The pain/discomfort domain of the Euroqol EQ-5D specifically has been validated among people living with chronic pain, and has demonstrated improved construct validity and responsiveness relative to other quality of life scales (Obradovic et al., 2013). Variable definitions are consistent with previous studies and refer to the six-month period prior to data collection (Lake, Walsh, et al., 2019; Reddon et al., 2020; Voon et al., 2014).

Statistical analysis

As a first step, the characteristics of the study sample, stratified by effective decreased opioid use when using cannabis, were analyzed using the χ^2 test for binary variables and the Wilcoxon rank sum test for continuous variables. Binary logistic regression models were used to estimate the unadjusted and adjusted Odds Ratios (OR) and 95% confidence intervals (CI) for variables associated with self-reported reductions in opioid use during periods of cannabis use. All covariates were retained in the adjusted models. The sub-analyses followed the same model building procedure as the primary analysis and analyzed

(1) the association between cannabis use to manage opioid cravings and opioid use among people living with moderate-severe pain based on the Euroqol EQ-5D pain/discomfort domain; and (2) the association between cannabis use to manage opioid cravings and opioid use among males and females. These sub-analyses were informed by previous studies demonstrating significant associations between cannabis use and opioid use among people living with chronic pain (Lake, Walsh, et al., 2019; Lucas et al., 2021; Okusanya et al., 2020), and significant gender differences in cannabis use behaviours (e.g., frequency), harms (e.g., prevalence of cannabis use disorder) and treatment-seeking behaviours (Imtiaz et al., 2016; Khan et al., 2013). All statistical analyses were performed using SPSS version 28 (IBM Corporation, New York, USA) and all tests of significance were two-sided with a significance threshold of $p < 0.05$.

RESULTS

A total of 205 individuals from the VIDUS ($n = 91$, 44.4%), ACCESS ($n = 47$, 22.9%) and ARYS ($n = 67$, 32.7%) cohorts completed the supplementary cannabis questionnaire and reported opioid use in the last six months, including 67 (32.7%) females, 76 (37.1%) reported BIPOC race and ethnicity and the median age was 39.9 years (interquartile range: 29.4–53.5). Cannabis use to manage opioid cravings was reported by 91 (44.4%) individuals and 118 (57.6%) individuals reported decreasing their opioid use through cannabis use (Table 1). Of those who reported cannabis use to manage opioid cravings, 62 (68.1%) reported self-assessed decreases in opioid use during periods of cannabis use while 29 (31.9%) did not report self-assessed decreases in opioid use during periods of cannabis use. Participants who reported using cannabis to manage opioid cravings and reported decreased opioid use during periods of cannabis use were more likely to reside in the DTES, access free cannabis substitution programs and were less likely to report licit employment than participants who reported using cannabis to manage opioid cravings and did not report decreased opioid use during periods of cannabis use ($p < 0.05$) (Supplementary Table 1).

Daily cannabis use was reported by 88 (43.1%) participants, 70 (34.5%) participants reported high-THC cannabis as the most commonly used ratio of cannabis products. Among the participants living with HIV ($n = 47$, 22.9%), 22 (46.8%) reported daily cannabis use, 21 (44.7%) reported moderate-severe pain and 22 (46.8%) reported using cannabis to manage opioid cravings. These distributions were not statistically significant from the participants who were HIV seronegative ($p > 0.05$).

In the unadjusted binary logistic regression analysis, using cannabis to manage opioid cravings (OR=2.21, 95% CI: 1.25, 3.93), daily cannabis use (OR=2.91, 95% CI: 1.10, 7.69) and membership to the ARYS cohort (OR=2.54, 95% CI: 1.14, 5.64) were significantly associated with self-assessed reductions in opioid use during periods of cannabis use (Table 2). In the adjusted analysis, cannabis use to manage opioid cravings (adjusted OR [aOR] =2.13, 95% CI: 1.07, 4.27), daily cannabis use (aOR=3.87, 95% CI: 1.16, 12.88) and female gender (aOR=2.80, 95% CI: 1.26, 6.22) were significantly associated with self-assessed reductions in opioid use during periods of cannabis use (Table 2).

In the first sub-analysis stratified by pain level, cannabis use to manage opioid cravings was only significantly associated with self-assessed decreases in opioid use among those living with moderate to severe pain (n = 101, 49.3%) (OR=4.44, 95% CI: 1.52, 12.97), and was not significantly associated with self-assessed decreases in opioid use among those low or no pain (n = 104, 50.7%) (OR=0.76, 95% CI: 0.26, 2.27) (Table 3). In the gender-stratified sub-analysis among males (n = 138, 67.3%) and females (n = 67, 32.7%), only daily cannabis use (OR=6.50, 95% CI: 1.31, 32.35) was significantly associated with self-assessed decreases in opioid use among males, while only cannabis use to manage opioid cravings (OR=8.19, 95% CI: 1.20, 55.81) was significantly associated with self-assessed decreases in opioid use among females (Table 4).

DISCUSSION

In the present study, we observed that cannabis use to manage opioid cravings was significantly associated with self-assessed decreases in opioid use during periods of cannabis use among a structurally marginalized population of PWUD. The sub-analysis indicated that this association was mainly driven by those living with moderate to severe pain and the association between cannabis use to manage opioid cravings and self-assessed decreases in opioid use was not statistically significant among those living with low or no pain. In the sub-analysis of males and females, cannabis use to manage opioid cravings was only associated with self-assessed decreases in opioid use among females, while only daily cannabis use was associated with self-assessed reductions in opioid use during periods of cannabis use among males. These findings add to the existing evidence evaluating the association between cannabis use and opioid-related outcomes among PWUD. While previous studies have examined the relationship between cannabis use and the frequency of unregulated opioid use (Kral et al., 2015; Lake, Walsh, et al., 2019), to our knowledge, this is the first study to analyze the association between the specific cannabis use motive of reducing opioid cravings and self-assessed changes in unregulated opioid use among PWUD.

The potential for cannabis to be used as a substitute for opioids is supported by epidemiological evidence showing that approximately 30% of medical cannabis users report cannabis substitution for opioids and cannabis use was associated with significant decreases (16–64%) in opioid use (Boehnke, Litinas, & Clauw, 2016; Lucas, 2017; Reiman et al., 2017). Among prospective cohort studies of PWUD in Canada, daily cannabis use has been linked to decreases in the frequency of unregulated opioid use and periods of cessation from injection opioid use (Lake, Walsh, et al., 2019; Reddon et al., 2021; Reddon et al., 2020). Our findings build on these studies by demonstrating that intentional cannabis use to manage opioid cravings was associated with self-perceived decreases in opioid use during periods of cannabis use and this was only significant among people living with pain. This indicates that the presence of pain may moderate the association between cannabis use to manage opioid cravings and self-assessed changes in the frequency of opioid use. Although there have been concerns about replacing one form of substance use for another, the benefits and risks associated with cannabis use should be evaluated in the context of other concurrent substance use among people who use unregulated drugs and are living with substance use disorders (Lucas, 2017). Existing studies estimate that fewer than 9–13% of people who use

cannabis report dependence, compared to 23–36% of people who use heroin, 21% people who use cocaine and 68% of people who use nicotine (Anthony, Warner, & Kessler, 1994; Leung, Chan, Hides, & Hall, 2020; Lopez-Quintero et al., 2011; Santiago Rivera, Havens, Parker, & Anthony, 2018). With the growing drug toxicity crisis in Canada and the United States, epidemiological evidence suggests that cannabis substitution could be used as a harm reduction strategy to address the public health impacts of opioid use (Hurd, 2017; Lake, Kerr, et al., 2019; Lucas, 2017; Mok et al., 2021).

Unfortunately, the majority of PWUD in Canada report significant barriers to accessing cannabis from regulated medical and non-medical systems, which has led to the emergence of peer-led harm reduction initiatives (e.g., The Cannabis Substitution Project, High Hopes Foundation) that distribute low- or no-cost cannabis to people living with substance dependence in an effort to divert them away from the contaminated illicit opioid supply (Lake et al., 2020; Valleriani et al., 2020). Qualitative studies have found these initiatives to have beneficial effects on the use of higher-risk substances (e.g., unregulated opioids and stimulants) (Paul et al., 2020; Valleriani et al., 2020) although further empirical evaluations are needed to elucidate their intended and unintended effects. We observed that participants who reported cannabis use to manage opioid cravings and reported self-assessed decreases in opioid use were more likely to reside in the DTES neighbourhood of Vancouver, report accessing free cannabis distribution programs and were less likely to report licit employment compared to participants who reported cannabis use to manage opioid cravings yet did not report self-assessed decreases in opioid use. This may suggest that the association between cannabis use to manage opioid cravings and self-assessed decreases in opioid use is stronger among people who are experiencing increased socio-economic marginalization and access community services to manage their substance use. Further studies will be needed to confirm or refute these observations.

While we did not find that the use of high-THC or high-CBD cannabis products was associated with self-assessed decreases in opioid use, several existing studies have found that the outcomes of cannabis consumption often depend on the cannabinoid composition of cannabis products (Kvamme et al., 2021). The lack of association in this study could be attributed to recall bias or error in reporting use of these products, or by inaccuracies in THC and CBD labels. A previous study of 10 Colorado dispensaries found that 70% of the samples overestimated the THC content by at least 15% (Schwabe, Johnson, Harrelson, & McGlaughlin, 2023). Inaccuracies have also been identified with topical products and cannabis from the unregulated market, whereby over 40% of the products tested were either under or over-labelled by at least 10% (Johnson, Kilgore, & Babalonis, 2022; Spindle et al., 2022). Nevertheless, there is preclinical evidence to suggest that THC and CBD may have some therapeutic benefits for people who use opioids. Preliminary human trials have found that administration of the synthetic cannabinoid dronabinol decreased the severity of opioid withdrawal (Bisaga et al., 2015; Lofwall, Babalonis, Nuzzo, Elayi, & Walsh, 2016). CBD has been found to attenuate opioid-induced reward, as well as reduce withdrawal symptoms and cue-induced cravings among people living with heroin dependence (Hurd et al., 2019; Ren, Whittard, Higuera-Matas, Morris, & Hurd, 2009).

Despite these findings, THC also carries risks of enhancing opioid reward self-administration and inducing acute cognitive impairments (Hurd, 2017). THC is a partial agonist of CB1 and CB2 cannabinoid receptors, and THC binding to CB1 receptors, which are colocalized with mu opioid receptors, produces feelings of reward (Hurd, 2017; Hurd et al., 2015). CB1 receptors mediate the antinociceptive properties of THC, which can be blocked through administration of CB1 antagonists and inverse agonists (Maguire & France, 2014). THC has also been shown to influence opioid peptide levels and enhance the reward, sensitivity and analgesic effects of other substances (Hurd et al., 2015). As a result, experimental human studies have found that co-administration of THC and opioids (e.g., hydromorphone) can increase abuse liability and the risk of adverse events (e.g., cognitive impairment) among healthy participants and these effects varied based on participant opioid sensitivity (Campbell et al., 2023; Dunn et al., 2021). Among PWUD, those living with concurrent opioid use disorder (OUD) and cannabis use disorder (CUD) in the United States experienced a higher likelihood of inpatient psychiatric admission compared to people with OUD only (De Aquino, Sofuoglu, Stefanovics, & Rosenheck, 2019). This may be attributed to increased abuse liability from the co-use of opioids and cannabinoids. Other potential adverse effects include cannabis withdrawal syndrome which affects nearly 50% of people with regular or dependent use of cannabis who cease use, as well as anxiogenic and other mental health sequelae (Bahji, Stephenson, Tyo, Hawken, & Seitz, 2020; Rey, Purrio, Viveros, & Lutz, 2012). As a result, the analgesic benefits of cannabis must be balanced with potential adverse effects such as abuse liability and acute cognitive impairment (Campbell et al., 2023; De Aquino et al., 2019; Dunn et al., 2021). Given that clinical guidelines for cannabis do not recommend cannabis use for chronic non-cancer pain or substance use disorders, elucidating the clinical and harm reduction potential of cannabis for people who use opioids will require additional experimental studies evaluating potential therapeutic benefits and adverse effects in the context of polysubstance use, in addition to the determining the accessibility of cannabis products with accurate and reliable cannabinoid compositions among marginalized PWUD.

The observation that cannabis use to manage opioid cravings was more strongly associated with self-assessed decreases in opioid use among people living with pain is supported by several studies and meta-analyses from a number of jurisdictions (Bradford et al., 2018; Lucas et al., 2019; Okusanya et al., 2020; Wen & Hockenberry, 2018). The prevalence of chronic pain among PWUD (48–60%) is significantly higher than among the general population (11–19%) and nearly two thirds of PWUD from a cohort study in Canada reported denial of prescription opioid analgesia from the medical system (Voon et al., 2015; Voon et al., 2018). In response, a significant proportion of PWUD report accessing the desired pain medication from illicit sources (40%) or acquiring unregulated opioids such as heroin (33%) to manage their pain after being denied prescription opioid analgesia (Voon et al., 2015). Accumulating research from cohort and survey studies in Canada and the United States has shown that therapeutic cannabis use to address chronic pain is common among PWUD and the general population, and is associated with reductions in the use of opioids and other prescription drugs (Lake, Walsh, et al., 2019; Lucas, 2017). A systematic review of cannabis use among patients affected by chronic pain found that 32–59% of individuals reported cannabis substitution for opioids, and using cannabis as an adjunct to

opioids resulted in a 64–75% decrease in opioid dosage (Okusanya et al., 2020). Given that chronic pain and denial of prescription opioid analgesia are common among PWUD, it is not surprising that cannabis use has emerged as a method of pain management among populations who experience structural barriers to regulated methods of opioid analgesia (Voon et al., 2015; Voon et al., 2018). Among a cohort of PWUD living with chronic pain, frequent cannabis use was associated with a 50% decrease in the odds of daily opioid use (Lake, Walsh, et al., 2019). Our findings add to the evidence that cannabis use to manage opioid cravings may have the potential to decrease opioid use among people living with chronic pain, which may also reduce the risk of exposure to fentanyl and the risk of overdose during the drug toxicity crisis (Socias et al., 2021).

The gender-specific associations between cannabis use patterns and opioid use that we observed may reflect documented differences in cannabis use and outcomes among males and females. Men have been found to initiate cannabis use at younger ages, are more likely to use frequently and in higher quantities, tend to have higher drug tolerance and are more likely to be long-term users (Cotto et al., 2010; Wagner & Anthony, 2002; Zhu & Wu, 2017). For these reasons, males may require more frequent cannabis use to produce effects that facilitate opioid substitution. We also found that cannabis use to manage opioid cravings was more strongly associated with self-assessed decreases in opioid use among females than males. This finding may be explained by observations that women are more likely to use cannabis for medical purposes while men are more likely to report recreational cannabis use (Cuttler, Mischley, & Sexton, 2016). Women may also experience stronger acute effects of cannabis at a given dose based on differences in tolerance (Cuttler et al., 2016). Although sex differences in cannabis use have decreased over time, investigating sex and gender-based differences in cannabis use and effectiveness among PWUD will be important to inform if and how cannabis-based interventions might be applied in the context of harm reduction, and to identify barriers to equitable cannabis access among marginalized populations.

There are several limitations that should be considered when interpreting the results of this study. The cohorts analyzed were not random samples of PWUD which may limit the generalizability of the findings to other settings. Since this study was cross-sectional, we cannot be certain about the directionality of these associations, whether the associations are durable over time, or if they were influenced by residual confounding. Self-reported measures of stigmatized behaviours such as substance use may have biased our results, although self-report among PWUD has demonstrated strong validity when compared to biomarker assessment (Ahmad, Jhajj, Stewart, Burghardt, & Bierman, 2014; Darke, 1998). It is also important to note that changes in opioid use were self-attributed with reference to periods of cannabis use and were not independently assessed. Study participants did not report if their cannabis use as recreational or medicinal and this distinction, or overlap, may have been associated with cannabis use behaviours that may have influenced our results (Turna et al., 2020). As this was an exploratory analysis that tested multiple hypotheses, additional studies are needed to confirm these associations in other samples of PWUD. Lastly, the inaccuracy of THC and CBD content labels may have introduced error into our measurement of these cannabinoids (Johnson et al., 2022; Schwabe et al., 2023; Spindle et al., 2022).

In summary, we observed that cannabis use to manage opioid cravings was significantly associated with self-assessed decreases in opioid use among PWUD. This association was only significant among people living with pain and the potential for cannabis to reduce opioid use in the context of chronic pain has been observed in several existing studies. This suggests that future studies of cannabis substitution for opioid use should measure and analyze the impact of pain, as not doing so may lead to equivocal findings when the effects of cannabis substitution may vary based on the prevalence of chronic pain. While monitoring the harms of expanding cannabis access and use are important public health priorities, the harms and potential benefits should be evaluated with consideration for other concurrent unregulated substance use, particularly during the drug toxicity crisis. Additional randomized controlled trials and longitudinal observational data will be helpful to clarify the outcomes of specific cannabis use patterns, such as substitution, with more certainty.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Declaration of Competing Interest

Hudson Reddon: None to declare.

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Table 1.

Characteristics of opioid users stratified by changes in opioid use during periods of cannabis use (n = 205).

Characteristic	Total *n* (%)	Decreased opioid use during periods of cannabis use		
		Yes 118 (57.6%) *n* (%)	No 87 (42.3%) *n* (%)	*p* - value
Age				
Median	39.9	39.9	39.9	0.670
IQR	(29.4 – 53.5)	(29.4 – 54.3)	(29.0 – 53.3)	
Gender				
Male	138 (67.3)	75 (63.6)	63 (72.4)	0.182
Female	67 (32.7)	43 (36.4)	24 (27.6)	
Race and ethnicity				
White	129 (62.9)	76 (64.4)	53 (60.9)	0.609
BIPOC	76 (37.1)	42 (35.6)	34 (39.1)	
Cohort				0.057
VIDUS	91 (44.4)	50 (42.4)	41 (47.1)	
ACCESS	47 (22.9)	34 (28.8)	13 (14.9)	
ARYS	67 (32.7)	34 (28.8)	33 (37.9)	
Employment [a]				
Yes	65 (31.7)	33 (28.0)	32 (36.8)	0.180
No	140 (68.3)	85 (72.0)	55 (63.2)	
DTES residence [a]				
Yes	108 (53.2)	64 (54.7)	44 (51.2)	0.618
No	95 (46.8)	52 (45.3)	42 (48.8)	
Access to free cannabis substitution programs [a]				
Yes	60 (29.3)	37 (31.4)	23 (26.4)	0.444
No	145 (70.7)	81 (68.6)	64 (73.6)	
Homelessness [a]				
Yes	48 (23.6)	27 (23.1)	21 (24.4)	0.824
No	155 (76.4)	90 (76.9)	65 (75.6)	
Pain [a]				
Moderate or severe	101 (49.3)	58 (49.2)	43 (49.4)	0.969
None or slight	104 (50.7)	60 (50.8)	44 (50.6)	
Opioid use [a]				
≥Daily	121 (59.3)	69 (58.5)	52 (60.5)	0.775
<Daily	83 (40.7)	49 (41.5)	34 (39.5)	
Cannabis use [a]				
<once/month	21 (10.2)	9 (7.6)	12 (13.8)	**0.011**
1–3 times/month	28 (13.7)	12 (10.2)	16 (18.4)	
once/week	24 (11.7)	9 (7.6)	15 (17.2)	
2–6 times/week	43 (21.0)	27 (22.9)	16 (18.4)	

Characteristic	Total *n* (%)	Decreased opioid use during periods of cannabis use		
		Yes 118 (57.6%) *n* (%)	**No 87 (42.3%) *n* (%)**	***p* - value**
≥daily	89 (43.4)	61 (51.7)	28 (32.2)	
High THC cannabis use [a]				
Yes	70 (34.5)	45 (38.8)	25 (28.7)	0.136
No	133 (65.5)	71 (61.2)	62 (71.3)	
High CBD cannabis use [a]				
Yes	19 (9.3)	12 (10.2)	7 (8.0)	0.604
No	186 (90.7)	106 (89.8)	80 (92.0)	
Cannabis use to manage opioid cravings [a]				
Yes	91 (44.4)	62 (52.5)	29 (33.3)	**0.006**
No	114 (55.6)	56 (47.5)	58 (66.7)	

Notes:

[a]Refers to activities in the 6 months prior to the follow-up interview, IQR=interquartile range, BIPOC=Black, Indigenous and people of colour, DTES=Downtown Eastside neighbourhood of Vancouver, Bold text refers to *P*-values <0.05, Not all cells may add up to 205 as participants may choose not to answer sensitive questions.

Table 2.

Logistic regression analysis of factors associated with decreased opioid use (n = 205).

	Unadjusted		Adjusted	
Characteristic	**OR (95% CI)**	***p* - value**	**OR (95% CI)**	***p* - value**
Age				
(per 5 years older)	1.02 (0.92, 1.14)	0.668	0.96 (0.79, 1.17)	0.678
Gender				
(female vs. male)	1.51 (0.83, 2.75)	0.183	2.80 (1.26, 6.22)	**0.011**
White ancestry				
(yes vs. BIPOC)	1.16 (0.66, 2.06)	0.610	1.74 (0.81, 3.76)	0.158
Cohort				
ACCESS vs. VIDUS	1.18 (0.63, 2.23)	0.601	1.42 (0.43, 4.65)	0.568
ARYS vs. VIDUS	2.54 (1.14, 5.64)	**0.022**	2.47 (0.68, 8.94)	0.169
Employment [a]				
(yes vs. no)	0.67 (0.37, 1.21)	0.181	0.56 (0.27, 1.14)	0.109
DTES residence [a]				
(yes vs. no)	1.75 (0.60, 5.11)	0.309	0.90 (0.41, 1.96)	0.782
Access to free cannabis substitution programs [a]				
(yes vs. no)	1.44 (0.51, 4.09)	0.493	0.75 (0.34, 1.67)	0.485
Homelessness [a]				
(yes vs. no)	0.93 (0.43, 1.79)	0.824	0.92 (0.41, 2.10)	0.847
Pain [a]				
(yes vs. no)	0.99 (0.57, 1.72)	0.969	0.89 (0.45, 1.75)	0.735
Cannabis use [a]				
<once/month	reference		reference	
1–3 times/month	1.00 (0.32, 3.14)	0.999	1.61 (0.42, 6.15)	0.488
once/week	0.80 (0.24, 2.65)	0.715	0.98 (0.26, 3.76)	0.976
2–6 times/week	2.25 (0.78, 6.51)	0.135	2.96 (0.82, 10.78)	0.099
≥daily	2.91 (1.10, 7.69)	**0.032**	3.87 (1.16, 12.88)	**0.028**
High THC cannabis use [a]				
(yes vs. no)	1.48 (0.81, 2.71)	0.201	1.68 (0.81, 3.48)	0.161
High CBD cannabis use [a]				
(yes vs. no)	1.28 (0.48, 3.39)	0.623	1.82 (0.32, 10.53)	0.503
Cannabis use to manage opioid cravings [a]				
(yes vs. no)	2.21 (1.25, 3.93)	**0.007**	2.13 (1.07, 4.27)	**0.032**

Notes: CI= confidence interval

[a]Refers to activities in the 6 months prior to the follow-up interview, BIPOC=Black, Indigenous and people of colour, DTES=Downtown Eastside neighbourhood of Vancouver, Bold text refers to *P*-values <0.05.

Table 3.

Logistic regression analysis of factors associated with decreased opioid use among people living with and without chronic pain (n = 205).

	Chronic pain			
	No (n = 104, 50.7%)		Yes (n = 101, 49.7%)	
Characteristic	**OR (95% CI)**	***p* - value**	**OR (95% CI)**	***p* - value**
Age				
(per 5 years older)	0.95 (0.72, 1.24)	0.703	0.89 (0.63, 1.27)	0.525
Gender				
(female vs. male)	1.81 (0.57, 5.74)	0.313	3.24 (0.85, 12.32)	0.084
White ancestry				
(yes vs. BIPOC)	1.82 (0.55, 5.99)	0.328	1.45 (0.43, 4.95)	0.550
Cohort				
ACCESS vs. VIDUS	1.05 (0.19, 5.72)	0.953	2.29 (0.30, 17.60)	0.667
ARYS vs. VIDUS	3.34 (0.54, 20.50)	0.193	2.75 (0.29, 25.73)	0.426
Employment [a]				
(yes vs. no)	0.62 (0.23, 1.70)	0.354	0.39 (0.11, 1.40)	0.149
DTES residence [a]				
(yes vs. no)	0.62 (0.20, 1.97)	0.422	1.22 (0.35, 4.21)	0.758
Access to free cannabis substitution programs [a]				
(yes vs. no)	0.87 (0.26, 2.92)	0.354	0.82 (0.24, 2.81)	0.149
Homelessness [a]				
(yes vs. no)	1.94 (0.51, 7.38)	0.330	0.67 (0.19, 2.34)	0.527
Cannabis use [a]				
<once/month	reference		reference	
1–3 times/month	1.37 (0.22, 8.45)	0.736	1.88 (0.14, 25.12)	0.633
once/week	0.88 (0.17, 4.72)	0.884	1.00 (0.08, 13.22)	0.999
2–6 times/week	1.81 (0.32, 10.21)	0.502	6.18 (0.49, 78.15)	0.160
≥daily	3.20 (0.71, 14.47)	0.131	4.91 (0.44, 54.58)	0.196
High THC cannabis use [a]				
(yes vs. no)	1.47 (0.51, 4.22)	0.477	2.07 (0.62, 6.89)	0.236
High CBD cannabis use [a]				
(yes vs. no)	0.49 (0.05, 5.31)	0.561	1.11 (0.78, 3.01)	0.974
Cannabis use to manage opioid cravings [a]				
(yes vs. no)	0.76 (0.26, 2.27)	0.626	4.44 (1.52, 12.97)	**0.006**

Notes: CI= confidence interval

[a]Refers to activities in the 6 months prior to the follow-up interview, BIPOC=Black, Indigenous and people of colour, DTES=Downtown Eastside neighbourhood of Vancouver, Bold text refers to *P*-values <0.05.

Table 4.

Logistic regression analysis of factors associated with decreased opioid use among males and females (*n* = 205).

	Males ***n*** **= 138 (67.3%)**		**Females** ***n*** **= 67 (32.7%)**	
Characteristic	**OR (95% CI)**	***p*** **- value**	**OR (95% CI)**	***p*** **- value**
Age				
(per 5 years older)	1.02 (0.81, 1.28)	0.869	0.73 (0.46, 1.17)	0.191
White ancestry				
(yes vs. BIPOC)	1.28 (0.48, 3.40)	0.624	3.28 (0.58, 18.55)	0.179
Cohort				
ACCESS vs. VIDUS	1.02 (0.24, 4.41)	0.182	3.35 (0.21, 53.43)	0.298
ARYS vs. VIDUS	2.94 (0.62, 14.00)	0.976	12.38 (0.40, 33.55)	0.392
Employment [a]				
(yes vs. no)	0.53 (0.22, 1.28)	0.156	0.74 (0.15, 3.70)	0.713
DTES residence [a]				
(yes vs. no)	0.79 (0.31, 2.00)	0.615	0.87 (0.14, 5.51)	0.882
Access to free cannabis substitution programs [a]				
(yes vs. no)	0.80 (0.30, 2.14)	0.651	1.53 (0.27, 8.51)	0.631
Homelessness [a]				
(yes vs. no)	0.70 (0.26, 1.87)	0.478	1.72 (0.23, 12.99)	0.599
Pain [a]				
(yes vs. no)	0.73 (0.31, 1.72)	0.465	1.11 (0.24, 5.20)	0.891
Cannabis use [a]				
<once/month	reference		reference	
1–3 times/month	1.41 (0.21, 9.44)	0.726	12.41 (0.68, 22.72)	0.090
once/week	1.46 (0.23, 9.09)	0.687	0.37 (0.02, 6.14)	0.489
2–6 times/week	5.20 (0.90, 29.95)	0.065	2.73 (0.16, 47.63)	0.491
≥daily	6.50 (1.31, 32.35)	**0.022**	2.99 (0.17, 51.27)	0.451
High THC cannabis use [a]				
(yes vs. no)	1.77 (0.74, 4.24)	0.198	1.98 (0.34, 11.41)	0.446
High CBD cannabis use [a]				
(yes vs. no)	3.34 (0.29, 38.88)	0.336	0.27 (0.01, 7.30)	0.437
Cannabis use to manage opioid cravings [a]				
(yes vs. no)	1.45 (0.62, 3.40)	0.392	8.19 (1.20, 55.81)	**0.032**

Notes: CI= confidence interval

[a]Refers to activities in the 6 months prior to the follow-up interview, BIPOC=Black, Indigenous and people of colour, DTES=Downtown Eastside neighbourhood of Vancouver, Bold text refers to *P*-values <0.05.