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Journal

Cannabis and Cannabinoid Research, 8(1)

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Publication Date

2023-02-01

DOI

10.1089/can.2021.0080

Peer reviewed

Cannabis and Cannabinoid Research
Volume 8, Number 1, 2023

DOI: 10.1089/can.2021.0080

The Cannabis-Dependent Relationship Between Methadone Treatment Dose and Illicit Opioid Use in a Community-Based Cohort of People Who Use Drugs

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Abstract

Background: Methadone maintenance treatment (MMT) is an effective treatment for opioid use disorder. However, subtherapeutic dosing may lead to continued opioid use by failing to suppress opioid withdrawal and craving. Preclinical and pilot experimental research suggests that cannabinoids may reduce opioid withdrawal and craving. We sought to test whether the association between low methadone dose and illicit opioid use differs according to concurrent cannabis use patterns.

Methods: Data for this study were derived from two community-recruited cohorts of people (≥18 years old) who use illicit drugs in Vancouver, Canada. We used generalized estimating equations to estimate the adjusted association between lower daily MMT dose (<90 mg/day) and daily illicit opioid use, testing for interaction between dose and daily cannabis use.

Results: Between December 2005 and December 2018, 1389 participants reported MMT enrolment and were included in the study. We observed a significant interaction ($p < 0.01$) between daily cannabis and lower MMT dose on concurrent daily illicit opioid use: lower MMT doses increased the odds of daily illicit opioid use by 86% (adjusted odds ratio [AOR] = 1.86, 95% confidence interval [CI] = 1.61–2.16) during periods of no or low-frequency cannabis use and by 30% during periods of daily cannabis use (AOR = 1.30, 95% CI = 1.01–1.67).

Discussion: This study provides preliminary observational evidence that cannabis may mitigate some of the negative effects of subtherapeutic MMT dosing, guiding future clinical investigations into the safety and efficacy of cannabis and cannabinoids as adjunct treatment for MMT.

Keywords: cannabis; methadone; opioid use disorder; opioids; opioid agonist treatment; cohort study

Introduction

Pharmacological management of opioid use disorder (OUD) with an opioid agonist, such as methadone or buprenorphine/naloxone, is an effective medication-based intervention to prevent opioid overdose.[1,2] While there are patient exceptions (e.g., older patients, patients with comorbid cardiovascular or respiratory disease), studies from diverse treatment settings demonstrate that higher methadone doses are strongly negatively correlated with continued use of illicit opioids.[3–6] However, many patients receive treatment doses that are suboptimal for the management

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of OUD. For instance, roughly one in five methadone patients in the United States are prescribed doses below the minimum recommended standard of 60 mg/day.[7]

Concurrent cannabis during OUD treatment is common, with prevalence of co-use typically ~50% in clinical studies of patients receiving methadone maintenance treatment (MMT).[8–12] Continued use of other substances (e.g., alcohol, opioids, cocaine, methamphetamine, benzodiazepines) while on medication-based treatment of OUD is often linked to worse clinical outcomes.[6,13,14] However, studies have produced inconsistent evidence of the impact of cannabis use during medication-based treatment for OUD, including MMT, with some reporting improvement in outcomes, others pointing to negative effects, and the rest yielding nonsignificant findings.[15] Emerging research among marginalized people who use illicit drugs (PWUD) from our study setting (Vancouver, Canada) and elsewhere has shown that cannabis is used for a wide range of therapeutic purposes, including pain management, sleep, stress, nausea, and appetite stimulation, management of substance use disorders, and substitution for other substances including opioids.[16,17] In a recent observational study involving PWUD living with pain, we observed that the odds of high-frequency illicit opioid use were halved among those engaging in daily cannabis use relative to nonusers.[18]

In evaluating the impact of cannabis use on treatment outcomes for OUD, few studies have considered the relationship between treatment dose and cannabis use frequency. There is a mounting rationale for examining the potential beneficial role of cannabis and its constituents in mitigating the association between drivers of opioid withdrawal and/or craving—such as treatment dose—and clinical outcomes during opioid agonist treatment—such as continued use of opioids.[19] Opioid withdrawal has overlapping symptomology with many of the common indications for medical cannabis use, including nausea and vomiting, insomnia, and enhanced pain sensitivity.[20] Experimentation with cannabis for the management of opioid withdrawal appeared in the medical literature as early as the 1940s,[21] and recent qualitative studies involving people who use illicit opioids describe the *ad hoc* strategy of using cannabis to curb opioid cravings and withdrawal during periods of transition from high- to low-intensity opioid use.[22,23] Recently, a small number of experimental studies among human subjects have presented evidence of reductions in severity of opioid withdrawal with the administration of delta-9-tetrahydrocannabinol (THC), the primary psychoactive component of cannabis,[24] and suppression of opioid cravings with cannabidiol (CBD), a nonintoxicating component of cannabis.[25] Some observational studies have noted significantly lower doses of medication-based treatment for OUD (i.e., methadone and buprenorphine) among cannabis-using patients,[11,26,27] possibly reflecting a strategy to supplement inadequate treatment doses with cannabis.[28]

Using up to 13 years of data from two community-recruited cohorts of PWUD in Vancouver, Canada, we aimed to examine the relationship between cannabis use, treatment dose, and illicit (i.e., unregulated or not-as-prescribed) opioid use during treatment among those enrolled in MMT. Rather than evaluating the independent relationship between cannabis use and opioid use during MMT, we sought to test the hypothesis that cannabis use reduces the magnitude of the widely established relationship between lower methadone treatment doses and illicit opioid use during treatment.

Materials and Methods

Study population and procedures

Data for this study were obtained from two open prospective cohorts of PWUD in Vancouver, Canada. The Vancouver Injection Drug Users Study (VIDUS) is composed of HIV-negative people who inject drugs, whereas the AIDS Care Cohort to evaluate Exposure to Survival Services (ACCESS) is composed of PWUD living with HIV. The studies have been ongoing since 1996 (VIDUS) and 2005 (ACCESS) and employ an open recruitment process (i.e., participants can be enrolled in the study at study inception or at any point afterward). Participants were recruited through collaboration with community services, extensive street outreach, and snowball sampling in areas across Vancouver's downtown core, with concentrated efforts in the Downtown Eastside (DTES), a low-income neighborhood with an open illicit drug market and widespread marginalization and criminalization of PWUD.

Eligibility criteria for the VIDUS include: (1) being HIV negative and (2) having used drugs by injection at least once in the 30 days before study enrolment. Eligibility criteria for ACCESS include: (1) being HIV positive and (2) using an illicit drug by injection or non-injection (other than or in addition to cannabis, which was a controlled substance in Canada until

October 17, 2018) in the 30 days before study enrolment. HIV serostatus is confirmed through serology. Additionally, participants in both studies must: (3) be at least 18 years of age; (4) reside in the Greater Vancouver Regional District; and (5) provide written informed consent. With the exception of HIV-specific study assessments for ACCESS participants, all study instruments and follow-up procedures described below are harmonized such that data can be pooled for statistical analyses and interpretation.

At study enrolment, participants completed two interviewer-administered questionnaires: the first questionnaire elicits information on a wide range of characteristics, exposures, and outcomes, including sociodemographic factors, current substance use patterns, health and social service utilization, and social- and structural-level exposures (e.g., incarceration); the second questionnaire elicits information on the participant's physical and mental health, disability, other health-related concerns, and general well-being. During the nurse assessment, blood is collected for HIV antibody testing (VIDUS) or HIV clinical monitoring (ACCESS) and hepatitis C serology (both cohorts). Participants were scheduled for a follow-up visit every 6 months after their baseline interview to allow for time-updated analyses of the information obtained at baseline. Participants received a $40 (CAD) honorarium for participation at each study visit. Ethical approval for both studies was granted by the University of British Columbia/Providence Health Care Research Ethics Board.

Analytic sample

From December 1, 2005, to November 30, 2018, we asked participants about their current and past 6-month enrolment in MMT for OUD at baseline and each 6-month follow-up interview. Eligible participants for this analysis were those who reported enrolment in MMT at least once during this study period. To estimate the relationship between methadone dose, cannabis use, and illicit opioid use during MMT, we further restricted the data from eligible participants to interview periods in which they reported current (i.e., at the time of interview) enrolment in MMT. While there are other pharmacological modalities to treat OUD, such as buprenorphine/naloxone, consistent dosage data were only collected for methadone as it was the dominant first-line treatment of OUD in Canada for the majority of the study period.

Measures

Outcome measure.

The outcome of interest was high-frequency illicit (i.e., unregulated or not-as-prescribed) opioid use during MMT. At each biannual interview, we asked participants about their recent (past 6 months) use of heroin and nonmedical use of pharmaceutical opioids (i.e., diverted, counterfeit, or not-as-prescribed use) by injection or non-injection (i.e., smoking, snorting, oral administration). Participants were provided a list of pharmaceutical opioids with corresponding pictures for ease of identification. Participants who indicated past 6-month use of either heroin or pharmaceutical opioids were asked to estimate the average frequency of use during that time (none, about once/month, about 2–3 times/month, about once/week, 2–3 times/week, and about once/day or more). Participants who endorsed using heroin or pharmaceutical opioids daily or more on average in the past 6 months were coded as "1" for the outcome (i.e., daily illicit opioid use) for that follow-up period. Daily use was chosen as the dichotomy point to indicate higher severity of OUD.[29] Of note, fentanyl powder became increasingly prevalent in the local illicit drug supply during the final 2–3 years of the study period but was often sold as heroin or "down." Thus, suspected fentanyl exposure was captured as heroin during this time.

Independent variables of interest.

The main exposures of interest were daily methadone dose (as the primary independent variable) and frequency of cannabis use (as the hypothesized effect measure modifier).

All participants who endorsed past 6-month MMT were asked to report their current daily dose in milliliters. In February 2014, the province changed the formulation of methadone provided under the provincial drug plan from a 1 mg/mL pharmacy-compounded formulation to a 10 mg/mL commercially available formulation (i.e., Methadose).[30] We multiplied all doses reported after February 2014 by 10 to standardize the variable to 1 mg/mL. We took the median treatment dose of all study observations (90 mg/day) to distinguish lower (<90 mg/day) from higher (≥ 90 mg/day) doses. This cut-point is supported by previous evidence showing more complete opioid blockade and improved treatment outcomes at doses of ≥ 100 mg/day.[13,31,32]

The relationship between methadone dose and illicit opioid use was hypothesized to differ by daily cannabis use. Similar to the measurement protocol for illicit opioid use, at each interview, participants were asked if they had used cannabis in the previous 6 months and

to estimate the average frequency of use (none, about once/month, about 2–3 times/month, about once/week, 2–3 times/week, and about once/day). As it was hypothesized that high-frequency use of cannabis would be required to observe an interaction effect (if one exists), cannabis use frequency was dichotomized into ≥ daily and < daily use.

Secondary variables. We made efforts to account for the potential confounding influence of several sociodemographic, substance use, and treatment-related variables known or *a priori* hypothesized to impact MMT-related treatment outcomes and which may be linked with MMT dose or cannabis use. Sociodemographic factors included sex (male vs. female), current age (per year older), racial identity (white vs. non-white), legal employment (yes vs. no), homelessness (defined as living on the street with no fixed address, consistent with previous analyses,[33] yes vs. no), and incarceration (yes vs. no). Substance use and health-related factors included HIV status, HIV serostatus (positive vs. negative), ≥ daily alcohol use (yes vs. no), and ≥ daily stimulant (crystal methamphetamine or crack/powder cocaine) use (yes vs. no). Treatment-related factors included calendar year of treatment (≥ 2014 vs. < 2014, corresponding to abrupt province-wide changes to the methadone formulation, which had widespread unintended impacts on opioid relapse[30]), percent time spent on MMT (measured as the cumulative percent of all interview periods, up to and including the current period, in which the participant was enrolled in MMT [categorized as > 75% vs. ≤ 75%]), and engagement in other substance use treatment (e.g., counseling, residential treatment). Aside from HIV status, which is confirmed through serology, all variables are self-reported. With the exception of sex and racial identity, all variables are time-varying and refer to the previous 6-month period at each study interview.

Statistical analyses

Each participant's baseline observation was considered the first interview period in which they reported current MMT enrolment. We first examined sociodemographic, substance use and health-related characteristics at baseline for all participants who reported current MMT enrolment at least once over the study period. We stratified these observations by daily cannabis use and tested group differences using the Pearson chi-square test (categorical variables) or the Wilcoxon rank-sum test (numeric variables).

Next, to examine the relationship between each independent variable and the outcome (daily illicit opioid use), we used bivariable and multivariable generalized estimating equations with an exchangeable correlation structure to account for possible correlation from repeated measures within individuals over time. First, the crude bivariable relationships with the outcome for lower MMT dose and cannabis use were examined separately. Then, we explored effect measure modification by including an interaction term between dose and cannabis. Following this, all hypothesized confounders outlined above were added to the model to estimate the adjusted association between methadone dose and daily illicit opioid use within each stratum of cannabis use. We checked the significance of effect measure modification using the likelihood ratio test.

All analyses were conducted in R (Version 3.6.3; R Foundation for Statistical Computing, Vienna, Austria) using RStudio (Version 1.2.5033). All p-values are two-sided.

Results

Between December 1, 2005, and November 30, 2018, a total of 2348 participants were recruited and completed at least one study interview. Of them, 1532 (65.2%) endorsed past 6-month MMT, and 1421 (92.8%) endorsed current MMT at least once. In total, 1389 (97.7%) current MMT patients completed all measures of interest including current MMT dose and were included in the analysis. These individuals contributed a median of 7 interviews (interquartile range [IQR]: 3–14) each, totaling 12,132 observations over 6066 person-years of follow-up. Baseline characteristics of this sample, stratified by daily cannabis use, are summarized in Table 1. As shown, 281 (20.2%) participants endorsed high-frequency cannabis use at baseline; this group was slightly younger (median age 40.1 vs. 41.7 years, $p = 0.010$) and had significantly higher male representation than the occasional/nonuser group (67.3% vs. 56.9%, $p = 0.002$). Past 6-month high-frequency (i.e., ≥ daily) opioid use was reported by 439 (31.6%) respondents at baseline and 770 (55.4%) respondents at least once throughout the study period, representing 1960 (16.2%) interviews.

Table 2 depicts the bivariable and multivariable relationships with high-frequency opioid use for the primary and secondary independent variables. As shown, at the bivariable level, lower daily MMT dose

Table 1. Baseline Characteristics of 1389 People Who Use Illicit Drugs Who Reported Current Methadone Maintenance Treatment in at Least One Study Interview Between December 1, 2005, and November 30, 2018

Characteristic	Overall ($n=1389$), *n* (%)	≥ Daily cannabis use,[a] *n* (%)		*p*-value
		Yes, $n=281$ (20.2%)	No, $n=1108$ (79.8%)	
Sociodemographic factors				
Sex				
Male	819 (59.0)	189 (67.3)	630 (56.9)	0.002
Female	570 (41.0)	92 (32.7)	478 (43.1)	
Age				
Median (IQR)	41.4 (34.6–47.9)	40.1 (33.7–46.7)	41.7 (34.9–48.4)	0.010
Racial identity				
White	848 (61.1)	178 (63.3)	670 (60.5)	0.415
Non-white	541 (38.9)	103 (36.7)	438 (39.5)	
Employment[a]				
Yes	255 (18.4)	58 (20.6)	197 (17.8)	0.308
No	1134 (81.6)	223 (79.4)	911 (82.2)	
Homelessness[a]				
Yes	435 (31.3)	80 (28.5)	355 (32.0)	0.280
No	954 (68.7)	201 (71.5)	753 (68.0)	
Incarceration[a]				
Yes	199 (14.3)	42 (14.9)	157 (14.2)	0.813
No	1190 (85.7)	239 (85.1)	951 (85.8)	
Substance use, health-related, and treatment-related factors				
Daily alcohol use[a]				
Yes	59 (4.2)	12 (4.3)	47 (4.2)	1.000
No	1330 (95.8)	269 (95.7)	1061 (95.8)	
Daily stimulant use[a]				
Yes	642 (46.2)	122 (43.4)	520 (46.9)	0.323
No	747 (53.8)	159 (56.6)	588 (53.1)	
Daily opioid use[a]				
Yes	439 (31.6)	83 (29.5)	356 (32.1)	0.445
No	950 (68.4)	198 (70.5)	752 (67.9)	
HIV serostatus				
HIV positive	529 (38.1)	107 (38.1)	422 (38.1)	1.000
HIV negative	860 (61.9)	174 (61.9)	686 (61.9)	
Other addiction treatment[a]				
Yes	269 (19.4)	54 (19.2)	215 (19.4)	1.000
No	1120 (80.6)	227 (80.8)	893 (80.6)	
Daily MMT dose[b]				
Lower (< 90 mg)	765 (55.1)	149 (53.0)	616 (55.6)	0.479
Higher (≥ 90 mg)	624 (44.9)	132 (47.0)	492 (44.4)	

[a]Refers to exposures in the previous 6 months.
[b]Daily MMT dose was reported at the time of interview.
IQR, interquartile range; MMT, methadone maintenance treatment.

(i.e., < 90 mg) was significantly associated with high-frequency illicit opioid use (odds ratio [OR] = 1.72, 95% confidence interval [CI] = 1.53–1.93, $p<0.001$), and high-frequency cannabis use was not significantly associated with the outcome (OR = 1.03, 95% CI = 0.89–1.20, $p=0.660$). The crude interaction between MMT dose and cannabis use was significant ($\chi^2=10.5$, $p=0.001$) such that during periods of no/low-frequency cannabis use, lower MMT dose increased the odds of daily illicit opioid use by 86% (OR = 1.86, 95% CI = 1.64–2.11, $p<0.001$), whereas during periods of high-frequency cannabis use, lower MMT dose increased the odds of daily illicit opioid use by 24% (OR = 1.24, 95% CI = 0.99–1.56; $p=0.057$). The interaction between dose and cannabis use remained significant ($\chi^2=6.72$, $p=0.010$) after adjusting for sociodemographic, substance use, and treatment-related factors (adjusted odds ratio [AOR] for < 90 mg vs. ≥ 90 mg dose during periods of low/no cannabis use = 1.86, 95% CI = 1.61–2.16, $p<0.001$; AOR for < 90 mg dose vs. ≥ 90 mg dose during periods of high-frequency cannabis use = 1.30, 95% CI = 1.01–1.67, $p=0.039$). As shown in Figure 1, the interaction can also be interpreted within each cannabis/dose combination by comparing against a single reference (< daily cannabis, higher dose). Against this common reference group, the adjusted odds of daily illicit opioid use associated with < 90 mg doses were still estimated to

Table 2. Bivariable and Multivariable Relationships Between Independent Variables and Daily Opioid Use Among 1389 People Who Use Illicit Drugs on Methadone Maintenance Treatment Between December 1, 2005, and November 30, 2018

	Daily illicit opioid use[a]			
Variable	OR (95% CI)	*p*-value	AOR (95% CI)	*p*-value
Treatment dose[b] (primary independent variable), pooled estimate				
Daily MMT dose (<90 mg/day vs. ≥90 mg/day)	1.72 (1.53–1.93)	<0.001	—	—
Cannabis use[a] (hypothesized effect measure modifier), pooled estimate				
Daily cannabis use (yes vs. no)	1.03 (0.89–1.20)	0.660	—	—
Treatment dose estimate[b], stratified by cannabis use[a,c]				
(Daily cannabis use = no): MMT dose (<90 mg/day vs. ≥90 mg/day)	1.86 (1.64–2.11)	<0.001	1.86 (1.61–2.16)	<0.001
(Daily cannabis use = yes): MMT dose (<90 mg/day vs. ≥90 mg/day)	1.24 (0.99–1.56)	0.057	1.30 (1.01–1.67)	0.039
Sociodemographic factors				
Sex (Male vs. female)	0.90 (0.76–1.08)	0.258	1.19 (0.99–1.43)	0.066
Age (per year increase)	0.96 (0.96– 0.97)	<0.001	0.96 (0.95–0.96)	<0.001
Racial identity (white vs. non-white)	0.83 (0.70–0.99)	0.034	0.95 (0.80–1.14)	0.591
Employed[a] (yes vs. no)	0.89 (0.80–1.00)	0.044	0.90 (0.79–1.02)	0.106
Homeless[a] (yes vs. no)	1.96 (1.72–2.23)	<0.001	1.68 (1.47–1.94)	<0.001
Incarcerated[a] (yes vs. no)	1.57 (1.33–1.85)	<0.001	1.24 (1.04–1.49)	0.020
Substance use and health-related factors				
Daily alcohol use[a] (yes vs. no)	1.11 (0.92–1.34)	0.285	1.04 (0.83–1.29)	0.754
Daily stimulant use[a] (yes vs. no)	2.14 (1.91–2.39)	<0.001	2.35 (2.07–2.68)	<0.001
HIV serostatus (positive vs. negative)	0.65 (0.55–0.78)	<0.001	0.75 (0.63–0.90)	0.002
Treatment-related factors				
Calendar year (≥2014 vs. <2014)	1.48 (1.34–1.64)	<0.001	2.40 (2.11–2.73)	<0.001
Percent time on MMT (>75% vs. ≤75%)	0.66 (0.57–0.76)	<0.001	0.71 (0.60–0.83)	<0.001
Other addiction treatment[a] (yes vs. no)	0.97 (0.86–1.10)	0.636	0.88 (0.76–1.00)	0.054

[a]Refers to the 6-month period preceding interview.
[b]Daily MMT dose was reported at the time of the interview.
[c]Measure of effect measure modification by cannabis use: unadjusted: $\chi^2 = 10.5$, $p = 0.001$; adjusted: $\chi^2 = 6.72$, $p = 0.010$.
AOR, adjusted odds ratio; CI, confidence interval; OR, odds ratio.

be lower for daily cannabis users (AOR = 1.47, 95% CI = 1.16–1.84) than for no/low-frequency cannabis users (AOR = 1.86, 95% CI = 1.61–2.16, Fig. 1).

Discussion

There has been growing and widespread interest in the possible therapeutic applications of cannabis and cannabinoids, including for the management of OUD.[19] We sought to explore whether cannabis use modifies the relationship between lower MMT dose and continued illicit opioid use during treatment. Our community-based study provides observational evidence to suggest that high-frequency cannabis use may temper the magnitude of the association between lower MMT dose and high-frequency illicit opioid use.

Previous clinical studies involving patients on MMT have not produced consistent findings that characterize cannabis as a preventative measure against opioid use during treatment. An early, small cross-sectional study of MMT patients noted significant negative correlations between number of days of cannabis use and heroin use in the past month, with daily cannabis users recording nearly a tenth of heroin use days compared with nonusers.[34] Since then, the majority of studies reporting on cannabis use among MMT patients have not found evidence of a significant relationship (positive or negative) with nonmedical opioid use.[4,8,10,12,28,35–40] Two notable limitations across many of these studies threaten the potential to detect a true relationship (positive or negative) between cannabis and opioid use during treatment if one were to exist: the measurement of cannabis use at treatment initiation only,[36–38,40] and the use of any (rather than frequent) as the minimal threshold for cannabis use.[4,12,35,36] Furthermore, the majority of these studies conceptualize cannabis as an independent variable (often one of many), rather than an exposure with the potential to modify the influence of another major risk factor for illicit opioid use. The current study addresses this gap by measuring cannabis use at 6-month intervals throughout MMT, and by conceptualizing cannabis as an effect measure modifier of MMT dose. Our analysis produced evidence in support of the hypothesis that concurrent high-frequency cannabis use modifies the relationship between MMT dose

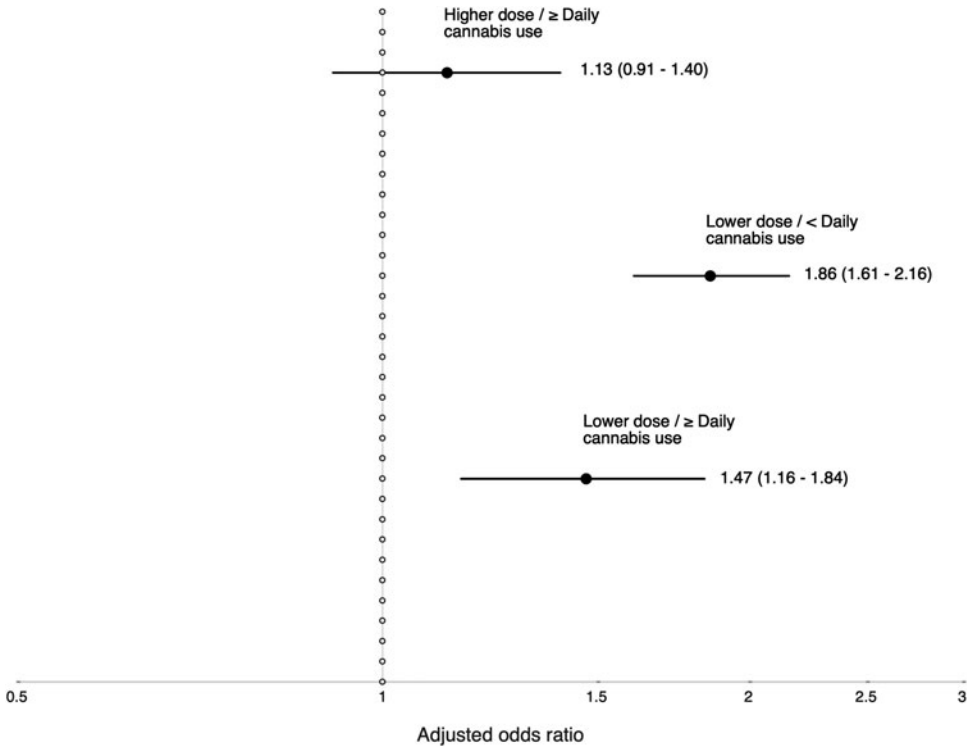

FIG. 1. Adjusted odds of daily illicit opioid use within strata of daily MMT dose and cannabis use (relative to higher dose/ < daily cannabis use) among 1389 PWUD on MMT in Vancouver, Canada, between December 1, 2005, and November 30, 2018. Estimates adjusted for sex, age, racial identity, employment, homelessness, incarceration, daily alcohol use, daily stimulant use, HIV serostatus, calendar year of treatment, percent time on treatment, MMT enrolment at study recruitment, and enrolment in other addiction treatment. AOR is shown on the log scale. AOR, adjusted odds ratio; PWUD, people who use illicit drugs; MMT, methadone maintenance treatment.

and high-frequency illicit opioid use—specifically, the strength of the negative association is elevated during periods of no or infrequent concurrent cannabis use.

Although the processes underlying the current findings are not immediately clear, one hypothesis is that cannabis is used to address certain negative effects associated with subtherapeutic dosing such as opioid craving and symptoms of withdrawal including anxiety, nausea/vomiting, and insomnia. Recent research demonstrates that this strategy is not uncommon among PWUD. In a small survey of PWUD in the United States, more than 60% reported using cannabis in an attempt to treat opioid withdrawal, and these participants reported significantly lower severity of withdrawal on cannabis use days.[41] Emerging research is exploring the potential role of cannabinoids in the treatment of OUD, including mitigation of craving and withdrawal. Two recent small randomized controlled trials recorded modest reductions in opioid withdrawal among participants who were randomized to receive a pharmaceutical preparation of THC (dronabinol) in conjunction with pharmacological management of OUD (oxycodone in one study,[42] extended-release naltrexone in the other).[24] Notably, as a secondary finding of the naltrexone study, participants who smoked cannabis throughout the trial experienced significant reductions in protracted withdrawal and exhibited longer study retention, regardless of randomized treatment status.[24]

At least two previous observational studies have probed the role of withdrawal in the relationship between cannabis and opioid use during MMT. Scavone et al. conducted a retrospective chart review of 91 OUD patients initiating MMT, comparing changes in opioid withdrawal severity over time by cannabis use

frequency, and found decreasing withdrawal severity with increasing frequency of cannabis use.[28] However, this finding did not translate to lower frequency of illicit opioid use among patients during either induction or stabilization phases.[28] In contrast to the study by Scavone et al., Epstein and Preston reported that past-week cannabis use was not significantly associated with next-week reductions in withdrawal severity in patients undergoing a methadone taper. Furthermore, in contrast to our study finding, Epstein and Preston did not observe a cannabis-dependent relationship between methadone dose and withdrawal severity.[35]

Our study was derived from a community-based cohort in which levels of past 6-month opioid withdrawal and craving could not be measured. The relationship between methadone dose, cannabis use, opioid craving and withdrawal, and opioid use is complex and needs to be evaluated with rigorous clinic-based observational research. This relationship would be most accurately tested through an experimental trial of cannabinoid administration in conjunction with medications for OUD. Considering missing data on withdrawal and craving and the observational nature of our study, the possibility remains that PWUD who engage in high-frequency cannabis use during MMT in the current setting differ by a latent factor from those who engage in less frequent or no cannabis use, creating a spurious interaction with dose in its relationship with opioid use. However, we attempted to measure and account for these potential differences through considering the influence of several other sociodemographic factors, substance use patterns, and treatment conditions; notably, we observed few significant differences according to frequency of cannabis use at baseline.

Despite that cannabis may be used by patients to support MMT outcomes, detection of THC and other drugs through routine patient urine drug screening can still result in treatment consequences including denial of take-home doses[43,44] and even treatment discontinuation in certain low-tolerance programs.[45] Our finding suggests that this practice is unlikely to benefit patients and may even exacerbate harm. High-frequency cannabis use among MMT patients may not necessarily indicate therapeutic intent; but, rather than taking evidence of cannabis use as grounds to penalize patients, this information should be used to ensure treatment is properly tailored to the patient. For example, in probing underlying motivations for high-frequency cannabis use, perceived relationship to MMT outcomes, and effects on mood, cognition, mental health, quality of life, and ability to function, clinicians could better guide patients toward their treatment goals—whether that involves the continued use of adjunctive cannabis or an alternative strategy. Indeed, cannabis is not benign and carries its own set of risks (e.g., cannabis use disorder). Importantly, as depicted in Figure 1, higher MMT doses play a critical role in preventing high-frequency illicit opioid use during treatment, regardless of high-frequency cannabis use. Thus, while our finding provides an intriguing signal that cannabis could contribute to mitigating certain negative outcomes associated with lower MMT doses, in learning of patient cannabis use, an obvious first step for clinicians would be to explore if the patient's dose meets a therapeutic threshold and whether it would be safe to increase the dose. In other words, our main finding should not detract from the primary goal of addressing opioid craving and withdrawal through adequate methadone dosing.

A major strength of this study was the ability to leverage up to 13 years of multiple MMT episodes per participant from over 1300 PWUD in a community setting with widespread low-barrier access to MMT. However, the observational nature of this study presents certain limitations that should be considered when interpreting these findings. First, it is not possible to randomly select PWUD from the community and, despite a diverse strategy for community recruitment, it cannot be guaranteed that the cohorts are generalizable to the entire population of PWUD. Second, the 6-month data collection structure prevented the ability to record certain details regarding timing and changes to variables of interest. Daily methadone dose was captured at the time of interview only, whereas cannabis and illicit opioid use were recorded as the average frequency of use in the previous 6 months. This limited our ability to account for patient treatment trajectories in relation to substance use patterns. While we attempted to control for MMT experience through quantifying the proportion of all study interviews to date in which the participant was enrolled in MMT, we could not account for whether the reported dose was the patient's stable long-term dose or a recently titrated one. Aside from HIV serostatus, all information is obtained via self-report; however, self-report of MMT dose, substance use, and associated risk behaviors among PWUD are generally valid and reliable.[46,47] Finally, as mentioned above, the study questionnaire did not capture levels of opioid withdrawal and craving

in the previous 6 months. This information is critical to understanding whether the current finding could be indicative of cannabis as an effective withdrawal self-management strategy for OUD. Furthermore, the questionnaire did not elicit information about certain dimensions of cannabis use that could better illuminate the findings, including cannabis composition (e.g., THC vs. CBD) and potency, modes of administration (e.g., smoking, oral ingestion), typical quantity used, and number of uses per day for the daily users.

The limitations of this study raise important issues to be addressed in the future research looking to investigate a therapeutic role of cannabinoids in the treatment of OUD. First, as new scientific discoveries emerge involving the endogenous cannabinoid system and its interaction with various cannabinoids and other bioactive components of cannabis preparations (e.g., terpenoids), it will be important to determine which (if any) cannabis-based products, doses, and modes of administration are optimal to administer as adjunct treatments to OUD pharmacotherapy. Given that THC is intoxicating and implicated in neurological reward pathways, there are concerns about the development of dependence and other harms with THC,[48] despite the promising findings of previous experimental research involving pharmaceutically isolated THC.[24,42] Cannabis with higher CBD content (e.g., equal amounts of THC and CBD) or isolated CBD are worth consideration in light of a recent study demonstrating that CBD reduced heroin cue-induced cravings and anxiety compared with placebo in abstinent patients with OUD.[25] There are no experimental studies to date that have evaluated the long-term application of cannabis (or a cannabinoid) as an adjunct treatment in the long-term pharmacological management of OUD; this will be a critical knowledge gap to address given that MMT is often a long-term treatment strategy. Finally, cannabis was legal for nonmedical use during only the final 6 weeks of this 13-year study period. It will be important to re-examine these relationships in the new era of legalized nonmedical cannabis, given that, in some settings, MMT patients are regularly tested for and expected to refrain from other substance use (including cannabis). While patients are unlikely to be penalized because of cannabis use in our setting, they may feel more comfortable and supported in discussing cannabis as a complementary treatment for OUD with their health care provider under a legal framework, and it is possible that the findings of this study would differ under those conditions.

Conclusions

In this community-based observational study of marginalized PWUD on MMT, cannabis use modified the effect measure between lower methadone doses and illicit opioid use such that the association was tempered during periods of high-frequency cannabis use. Cannabis use did not render the association nonsignificant or reverse its direction, reaffirming the importance of prescribing treatment doses that meet the therapeutic threshold regardless of concurrent cannabis use. Our finding is suggestive of a possible therapeutic role of cannabis for some patients in the treatment of OUD, but further research is needed to determine causality and elucidate potential underlying pathways including suppression of opioid craving and withdrawal. Our study provides preliminary evidence to guide future clinic-based and experimental investigation into the possible adjunctive administration of cannabis for medication-based management of OUD.

Acknowledgment

The authors would like to thank the study participants as well and past and present study staff.

Author Disclosure Statement

M.-J.M. is the Canopy Growth professor of cannabis science at the University of British Columbia (UBC), a position created from unstructured arms' length gifts to the university from Canopy Growth Corporation, a licensed producer of cannabis, and the Government of British Columbia's Ministry of Mental Health and Addictions. UBC has also received unstructured funding from NG Biomed, Ltd., an applicant to the Canadian federal government for a license to produce cannabis, to support M.-J.M. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the article, or in the decision to publish the results. M.-J.M. and M.E.S. were awarded funds by the Canadian Institutes of Health Research to study the safety and feasibility of co-dispensing tetrahydrocannabinol with methadone; Tilray will provide the study drug. Z.D.C. reports consultancy with GB Sciences and Beckley Canopy Therapeutics and serving on the scientific advisory board of FSD Pharma. All other authors declare no conflicts of interest.

Funding Information

This study was funded by the U.S. National Institutes of Health (ACCESS: U01-DA021525; VIDUS: U01-

DA038886). Study funders had no role in the study design, data collection or analysis, interpretation of the findings, or article writing/publishing. S.L. is supported through doctoral awards from the Canadian Institutes of Health Research (CIHR) and the Pierre Elliott Trudeau Foundation. T.K. is supported by a CIHR Foundation Grant. M.E.S. is supported by a Michael Smith Foundation for Health Research (MSFHR)/St. Paul's Hospital Foundation Scholar Award. K.H. is supported by a CIHR New Investigator Award (MSH-141971), a MSFHR Scholar Award, and the St. Paul's Foundation. N.F. is supported by a MSFHR/St. Paul's Hospital Foundation Scholar Award and the Philip Owen Professorship in Addiction Medicine. M.-J.M. is supported by the U.S. National Institutes of Health (U01-DA0251525), a New Investigator Award from CIHR and a Scholar Award from MSFHR.

References

1. Wakeman SE, Larochelle MR, Ameli O, et al. Comparative effectiveness of different treatment pathways for opioid use disorder. JAMA Netw Open. 2020;3:e1920622.
2. Krawczyk N, Mojtabai R, Stuart EA, et al. Opioid agonist treatment and fatal overdose risk in a state-wide US population receiving opioid use disorder services. Addiction. 2020;115:1683–1694.
3. Strain EC, Stitzer ML, Liebson IA, et al. Methadone dose and treatment outcome. Drug Alcohol Depend. 1993;33:105–117.
4. Proctor SL, Copeland AL, Kopak AM, et al. Outcome predictors for patients receiving methadone maintenance treatment: findings from a retrospective multi-site study. J Subst Use. 2016;21:601–613.
5. Swensen G, Ilett KF, Dusci LJ, et al. Patterns of drug use by participants in the Western Australian methadone program, 1984–1991. Med J Australia. 1993;159:373–376.
6. Hser Y-I, Saxon AJ, Huang D, et al. Treatment retention among patients randomized to buprenorphine/naloxone compared to methadone in a multi-site trial. Addiction. 2014;109:79–87.
7. D'Aunno T, Pollack HA, Frimpong JA, et al. Evidence-based treatment for opioid disorders: a 23-year national study of methadone dose levels. J Subst Abuse Treat. 2014;47:245–250.
8. Epstein DH, Preston KL. Does cannabis use predict poor outcome for heroin-dependent patients on maintenance treatment? Past findings and more evidence against. Addiction. 2003;98:269–279.
9. Wasserman DA, Weinstein MG, Havassy BE, et al. Factors associated with lapses to heroin use during methadone maintenance. Drug Alcohol Depend. 1998;52:183–192.
10. Weizman T, Gelkopf M, Melamed Y, et al. Cannabis abuse is not a risk factor for treatment outcome in methadone maintenance treatment: a 1-year prospective study in an Israeli clinic. Aust N Z J Psychiatry. 2004; 38:42–46.
11. Zielinski L, Bhatt M, Sanger N, et al. Association between cannabis use and methadone maintenance treatment outcomes: an investigation into sex differences. Biol Sex Differ. 2017;8:8.
12. Somers CJ, O'Connor J. Retrospective study of outcomes, for patients admitted to a drug treatment centre board. Irish Med J. 2012;105:295–298.
13. Peles E, Schreiber S, Sason A, et al. Similarities and changes between 15- and 24-year survival and retention rates of patients in a large medical-affiliated methadone maintenance treatment (MMT) center. Drug Alcohol Depend. 2018;185:112–119.
14. Sullivan LE, Moore BA, O'Connor PG, et al. The association between cocaine use and treatment outcomes in patients receiving office-based buprenorphine/naloxone for the treatment of opioid dependence. Am J Addict. 2010;19:53–58.
15. Lake S, St. Pierre M. The relationship between cannabis use and patient outcomes in medication-based treatment of opioid use disorder: a systematic review. Clin Psychol Rev. 2020;82:101939.
16. Lake S, Nosova E, Buxton J, et al. Characterizing motivations for cannabis use in a cohort of people who use illicit drugs: a latent class analysis. PLoS One. 2020;15:e0233463.
17. Ceasar RC, Kral AH, Simpson K, et al. Factors associated with health-related cannabis use intentions among a community sample of people who inject drugs in Los Angeles and San Francisco, CA 2016 to 2018. Drug Alcohol Depend. 2020;219:108421.
18. Lake S, Walsh Z, Kerr T, et al. Frequency of cannabis and illicit opioid use among people who use drugs and report chronic pain: a longitudinal analysis. PLoS Med. 2019;16:e1002967.
19. Scavone JL, Sterling RC, Van Bockstaele EJ. Cannabinoid and opioid interactions: implications for opiate dependence and withdrawal. Neuroscience. 2013;248:637–654.
20. Pergolizzi JV, Jr., Raffa RB, Rosenblatt MH. Opioid withdrawal symptoms, a consequence of chronic opioid use and opioid use disorder: current understanding and approaches to management. J Clin Pharm Ther. 2020; 45:892–903.
21. Grinspoon L. Marihuana reconsidered. Harvard University Press, Cambridge, MA, 1971.
22. Wenger LD, Lopez AM, Comfort M, et al. The phenomenon of low-frequency heroin injection among street-based urban poor: drug user strategies and contexts of use. Int J Drug Policy. 2014;25:471–479.
23. Boeri M, Pereira E, Minkova A, et al. Green hope: perspectives on cannabis from people who use opioids. Sociol Inq. 2021;91:668–695.
24. Bisaga A, Sullivan MA, Glass A, et al. The effects of dronabinol during detoxification and the initiation of treatment with extended release naltrexone. Drug Alcohol Depend. 2015;154:38–45.
25. Hurd YL, Spriggs S, Alishayev J, et al. Cannabidiol for the reduction of cue-induced craving and anxiety in drug-abstinent individuals with heroin use disorder: a double-blind randomized placebo-controlled trial. Am J Psychiatry. 2019;176:911–922.
26. Bagra I, Krishnan V, Rao R, et al. Does cannabis use influence opioid outcomes and quality of life among buprenorphine maintained patients? A cross-sectional, comparative study. J Addict Med. 2018;12: 315–320.
27. Franklyn AM, Eibl JK, Gauthier GJ, et al. The impact of cannabis use on patients enrolled in opioid agonist therapy in Ontario, Canada. PLoS One. 2017;12:e0187633.
28. Scavone JL, Sterling RC, Weinstein SP, et al. Impact of cannabis use during stabilization on methadone maintenance treatment. Am J Addict. 2013;22:344–351.
29. Hser YI, Huang D, Saxon AJ, et al. Distinctive trajectories of opioid use over an extended follow-up of patients in a multisite trial on buprenorphine + naloxone and methadone. J Addict Med. 2017;11:63–69.
30. Socías ME, Wood E, McNeil R, et al. Unintended impacts of regulatory changes to British Columbia Methadone Maintenance Program on addiction and HIV-related outcomes: an interrupted time series analysis. Int J Drug Policy. 2017;45:1–8.
31. Lappalainen L, Nolan S, Dobrer S, et al. Dose-response relationship between methadone dose and adherence to antiretroviral therapy among HIV-positive people who use illicit opioids. Addiction. 2015;110:1330–1339.
32. Donny EC, Walsh SL, Bigelow GE, et al. High-dose methadone produces superior opioid blockade and comparable withdrawal suppression to lower doses in opioid-dependent humans. Psychopharmacology (Berl). 2002;161:202–212.
33. Milloy MJ, Kerr T, Bangsberg DR, et al. Homelessness as a structural barrier to effective antiretroviral therapy among HIV-seropositive illicit drug users in a Canadian setting. AIDS Patient Care STDs. 2012;26:60–67.
34. Best D, Gossop M, Greenwood J, et al. Cannabis use in relation to illicit drug use and health problems among opiate misusers in treatment. Drug Alcohol Rev. 1999;18:31–38.
35. Epstein DH, Preston KL. No evidence for reduction of opioid-withdrawal symptoms by cannabis smoking during a methadone dose taper. Am J Addict. 2015;24:323–328.
36. Levine AR, Lundahl LH, Ledgerwood DM, et al. Gender-specific predictors of retention and opioid abstinence during methadone maintenance treatment. J Subst Abuse Treat. 2015;54:37–43.

37. Lions C, Carrieri MP, Michel L, et al. Predictors of non-prescribed opioid use after one year of methadone treatment: an attributable-risk approach (ANRS-Methaville trial). Drug Alcohol Depend. 2014;135:1–8.
38. Nava F, Manzato E, Lucchini A. Chronic cannabis use does not affect the normalization of hypothalamic-pituitary-adrenal (HPA) axis induced by methadone in heroin addicts. Prog Neuropsychopharmacol Biol Psychiatry. 2007;31:1089–1094.
39. Nirenberg TD, Liepman MR, Cellucci T, et al. Cannabis versus other illicit drug use among methadone maintenance patients. Psychol Addict Behav. 1996;10:222–227.
40. Saxon AJ, Wells EA, Fleming C, et al. Pre-treatment characteristics, program philosophy and level of ancillary services as predictors of methadone maintenance treatment outcome. Addiction. 1996;91:1197–1209.
41. Bergeria CL, Huhn AS, Dunn KE. The impact of naturalistic cannabis use on self-reported opioid withdrawal. J Subst Abuse Treat. 2020;113:108005.
42. Lofwall MR, Babalonis S, Nuzzo PA, et al. Opioid withdrawal suppression efficacy of oral dronabinol in opioid dependent humans. Drug Alcohol Depend. 2016;164:143–150.
43. Centre for Addiction and Mental Health (CAMH). Methadone maintenance client handbook, revised. 2008. Available from: https://www.porticonetwork.ca/documents/489955/0/Methadone+Maintenance+treatment+client+handbook+PDF/e04600c3-d0c1-47e1-9a25-346a66967a77. Accessed December 19, 2019.
44. Substance Abuse and Mental Health Services Administration (SAHMSA). Federal guidelines for opioid treatment programs. 2015. Available from: http://store.samhsa.gov/product/Federal-Guidelines-for-Opioid-Treatment-Programs/PEP15-FEDGUIDEOTP. Accessed October 20, 2019.
45. McElrath K. Medication-assisted treatment for opioid addiction in the United States: critique and commentary. Subst Use Misuse. 2018;53:334–343.
46. Darke S. Self-report among injecting drug users: a review. Drug Alcohol Depend. 1998;51:253–263.
47. Langendam MW, van Haastrecht HJ, van Ameijden EJ. The validity of drug users' self-reports in a non-treatment setting: prevalence and predictors of incorrect reporting methadone treatment modalities. Int J Epidemiol. 1999;28:514–520.
48. Wiese B, Wilson-Poe AR. Emerging evidence for cannabis' role in opioid use disorder. Cannabis Cannabinoid Res. 2018;3:179–189.

Cite this article as: Lake S, Kerr T, Buxton J, Walsh Z, Cooper ZD, Socías ME, Fairbairn N, Hayashi K, Milloy M-J (2023) The cannabis-dependent relationship between methadone treatment dose and illicit opioid use in a community-based cohort of people who use drugs, *Cannabis and Cannabinoid Research* 8:1, 155–165, DOI: 10.1089/can.2021.0080.

Abbreviations Used

ACCESS = AIDS Care Cohort to evaluate Exposure to Survival Services
AOR = adjusted odds ratio
CBD = cannabidiol
CI = confidence interval
IQR = interquartile range
MMT = methadone maintenance treatment
OR = odds ratio
OUD = opioid use disorder
PWUD = people who use illicit drugs
THC = delta-9-tetrahydrocannabinol
VIDUS = Vancouver Injection Drug Users Study