Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Cannabis use is associated with reduced risk of exposure to fentanyl among people on opioid agonist therapy during a community-wide overdose crisis

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ARTICLE INFO

Keywords:
Cannabis
Opioid use disorder
Opioid agonist therapy
Fentanyl

ABSTRACT

Background: The ongoing opioid overdose crisis is driven largely by exposure to illicitly-manufactured fentanyl. Preliminary observational and experimental research suggests that cannabis could potentially play a role in reducing use of prescription opioids among individuals with chronic pain. However, there is limited data on the effects of cannabis on illicit opioid consumption, particularly fentanyl, especially among individuals on opioid agonist therapy (OAT). We sought to assess the longitudinal association between cannabis use and exposure to fentanyl among people on OAT.

Methods: Data were drawn from two community-recruited prospective cohorts of people who use drugs in Vancouver, Canada. We used generalized linear mixed-effects modeling, adjusted by relevant confounders, to investigate the relationship between cannabis use and recent fentanyl exposure (both assessed by urine drug testing) among participants on OAT between 2016 and 2018.

Results: Among the 819 participants on OAT who contributed 1989 observations over the study period, fentanyl exposure was common. At the baseline interview, fentanyl was detected in a majority of participants (431, 53 %), with lower prevalence among individuals with urine drug tests positive for tetrahydrocannabinol (47 vs. 56 %, $p = 0.028$). Over all study interviews, cannabis use was independently associated with reduced likelihood of being recently exposed to fentanyl (Adjusted Prevalence Ratio = 0.91, 95 % Confidence Interval: 0.83 – 0.99).

Conclusions: Participants on OAT using cannabis had significantly lower risk of being exposed to fentanyl. Our findings reinforce the need for experimental trials to investigate the potential benefits and risks of controlled cannabinoid administration for people on OAT.

1. Introduction

The opioid overdose crisis in the United States (U.S.) and Canada remains a pressing public health challenge, one fueled largely by the widespread contamination of the illicit drug supply with illicitly-manufactured fentanyl (hereafter referred to as fentanyl) and related analogues. In 2018, fentanyl was involved in approximately two-thirds of the over 47,000 opioid-related deaths in the U.S. (Ahmad et al., 2019), and around three-quarters of the almost 4,600 opioid-related deaths in Canada (Special Advisory Committee on the Epidemic of Opioid Overdoses, September 2019). Within Canada, the province of British Columbia has been particularly affected by the rapid increase of fentanyl within the drug supply, as evidenced by the more than 1,500 overdose deaths in 2018 (31 per 100,000 people compared to a national average of 12.3) of which fentanyl was detected in 87 % (Special Advisory Committee on the Epidemic of Opioid Overdoses, September 2019).

At the clinical level, the primary intervention to reduce the risk of opioid overdose for people with opioid use disorder is engagement in opioid agonist therapy (OAT), typically methadone or buprenorphine/naloxone. Although the mortality benefits of OAT are well established (Sordo et al., 2017), there is limited data on the effectiveness of these medications in the context of the fentanyl crisis (Stone et al., 2018; Wakeman et al., 2019). Recent studies have documented fentanyl exposure rates among OAT clients ranging between 38 % and 71 % (Arfken et al., 2017; Jones et al., 2018; Stone et al., 2018; Wakeman

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https://doi.org/10.1016/j.drugalcdep.2020.108420
Received 3 June 2020; Received in revised form 14 October 2020; Accepted 31 October 2020

et al., 2019), confirming that many people continue to use illicit opioids while on OAT. These figures, in turn, underscore the need to identify novel strategies to support people who are engaged in OAT and are seeking to reduce or eliminate exposure to fentanyl to decrease their risk of overdose and death.

In this context, there has been increasing interest in the potential role of cannabinoids to address the escalating opioid overdose crisis. This interest has been sparked by a number of studies that have found links between licit cannabis availability (through medical and recreational cannabis laws) or cannabis use with reduced opioid use and related harms (Bachhuber et al., 2014; Bradford et al., 2018; Campbell et al., 2018; Shi, 2017; Wen and Hockenberry, 2018). These findings are also consistent with surveys of medical cannabis patients documenting substitution of opioids with cannabis, often in the context of undertreated pain (Boehnke et al., 2016; Lucas and Walsh, 2017). However, these studies have limitations, including potential ecological fallacy, and that most epidemiological studies were cross-sectional and evaluated pain-related outcomes, including prescription opioid use (Campbell et al., 2018). Further, they have limited applicability to individuals with opioid use disorder, a population bearing one of the heaviest burdens of overdose morbidity and mortality. In fact, the evidence for the impacts of cannabis use on illicit opioid use in this population, particularly those on OAT, is highly limited, according to a recent systematic review (McBrien et al., 2019). In addition, studies included in this review were conducted before the proliferation of fentanyl and limited to methadone-based OAT, further limiting its applicability in the current state of the overdose crisis and newer OAT alternatives. This question is highly relevant to contemporary clinical practice given the growth in medical cannabis use internationally but also since traditional OAT models have often taken a punitive approach to any drug use for individuals on OAT. Therefore, there is a critical need for more prospective individual-level research to better understand the relationship between cannabis and illicit opioid use and overdose risk in the fentanyl era. The present study aims to address this knowledge gap by investigating the relationship between cannabis use and fentanyl exposure among people on OAT, in Vancouver, Canada, a setting with an ongoing opioid overdose crisis caused by the widespread contamination of the illicit drug supply with fentanyl.

2. Methods

2.1. Study design and sample

Data for this study were drawn from two harmonized community-recruited prospective cohorts of PWUD in Vancouver, Canada, that have been ongoing since 1996: The Vancouver Injection Drug Users Study (VIDUS) and the AIDS Care Cohort to evaluate Exposure to Survival Services (ACCESS) study. Study eligibility and procedures have been described in detail elsewhere (Strathdee et al., 1998; Wood et al., 2008). In brief, VIDUS consists of HIV-negative adults (18 years and older) who report injecting drugs in the month prior to enrolment; and ACCESS of HIV-positive adults who report using illicit substances (other than or in addition to cannabis, which was legalized for recreational use on October 17, 2018) in the previous month at enrolment. Recruitment occurs through extensive community outreach in the Greater Vancouver Regional District, word of mouth and self-referral.

After providing written informed consent, participants complete an interviewer-administered questionnaire that elicits information on socio-demographics, substance use patterns, health care access, and other relevant social-structural exposures at baseline and every six months thereafter. In addition, at each study visit, participants undergo HIV testing (i.e., antibody testing or clinical monitoring of plasma HIV-1 RNA viral loads, CD4 counts and related measures) and HCV antibody testing, as appropriate. Since June 2016, participants also provide a urine sample for drug testing using BTNX Rapid Response™Multi-Drug Test Panel (Markham, ON, Canada). Substances screened for include (calibrator, cut-off value in ng/mL): fentanyl (fentanyl, 100, and norfentanyl, 20); opiates, including morphine, heroin, codeine (morphine, 100); methadone (2-Ethylidine-1, 5-dimethyl-3, 3-diphenylpyrrolidine [EDDP], 100); buprenorphine (BUP-3-D-Glucoronide, 10); oxycodone (oxycodone, 100); tetrahydrocannabinol (11-nor-Δ9-THC-9 COOH [THC], 50), a phytocannabinoid and the primary psychoactive constituent of cannabis; cocaine (benzoylecgonine, 150); amphetamine/methamphetamine (d-amphetamine, 1000); and benzodiazepine (oxazepam, 300). According to the manufacturer, the accuracy of test results (i.e., % of agreement with gas chromatography/ mass spectrometry [GC/MS) is >95 % for all the substances. Participants receive a CAD$ 40 honorarium at each study visit. The VIDUS and ACCESS studies have received approval by University of British Columbia/Providence Health Care Research Ethics Board.

For the purposes of the present study, the analytical sample was restricted to observations where participants reported being on OAT in the prior six months (i.e., methadone, buprenorphine/naloxone, slow-release oral morphine, injectable diacetylmorphine or hydromorphone) and had data from a matching urine drug test (UDT). We included observations between this December 1, 2016 and November 30, 2018.

2.2. Measures

The primary outcome of interest was recent exposure to fentanyl, defined as having a positive UDT for fentanyl. The main explanatory variable was recent use of cannabis, defined as having a positive UDT for THC. We also considered a number of covariates that were hypothesized to potentially confound the association between recent use of cannabis and recent fentanyl exposure. These included socio-demographic characteristics (age, gender, race, highest level of education); comorbidities (HIV infection, pain-related function and intensity assessed with the Brief Pain inventory [BPI] interference and severity scale, respectively (Dennis et al., 2016)), and anxiety and depression in the past seven days, assessed by their respective PROMIS short form measures (Johnston et al., 2016)); type of OAT enrolled in the last six months (methadone, buprenorphine/naloxone, slow-release oral morphine, injectable diacetylmorphine or hydromorphone, other/unknown); recent use/exposure to other substances assessed by UDT as described above; as well as structural-level exposures in the previous six months (homelessness and incarceration). Both BPI scales yield scores ranging from 0 to 10, where higher scores mean worse symptoms (Dennis et al., 2016). Similarly, PROMIS short forms scales for depression and anxiety range between 8 and 40, and between 7 and 35, respectively. These raw scores are then converted into standardized T-scores for interpretation, with higher scores indicating greater presence of symptoms. We dichotomized the depression and anxiety variables at T-scores ≥ 60, indicating moderate/severe depression or anxiety (Johnston et al., 2016). Except for socio-demographic variables, all other variables were time-updated and referred to the six-month period prior to each study interview.

2.3. Statistical analysis

First, we described the study sample characteristics, stratified by recent use of cannabis at the beginning of the study period, using Pearson χ^2 test for categorical variables and Wilcoxon rank-sum test for continuous variables. Next, we examined bivariable relationships between recent cannabis use and all other covariates with recent fentanyl exposure. Generalized estimating equations modeling (GEE) with a logit-link function was used to account for repeated measurements from the same participants over time. To estimate the independent effect of recent cannabis use on recent exposure to fentanyl among participants on OAT, we fit a multivariable GEE using all covariates regardless of bivariable association.

To assess the robustness of our estimate of cannabis use and fentanyl exposure from our multivariable model, we conducted two sub-analyses

Table 1
drugs on OAT, stratified by recent exposure to fentanyl, Vancouver, Canada (2016–2018).

	Total, n (%) (N = 819)	UDT Fentanyl[a], n (%)		p - value
		Negative (n = 388, 47%)	Positive (n = 431, 53%)	
UDT positive for THC[a]	533 (66)	151 (39)	135 (31)	0.028
Sociodemographics				
Age (median, IQR)	48 (38–55)	51 (45–57)	43 (35–51)	< 0.001 [d]
Male gender	467 (57)	231 (60)	236 (55)	0.155
White race	489 (60)	238 (61)	251 (58)	0.352
High school education or higher	386 (47)	180 (46)	206 (48 %)	0.777
Comorbidities				
HIV positive	283 (35)	103 (36.0)	180 (33.8)	0.571
BPI severity scale (med, IQR)[a], [b]	1 (0–6)	1 (0–6)	1 (0–6)	0.666[d]
BPI interference scale (med, IQR)[a]	0 (0–5)	0 (0–5)	0 (0–6)	0.381[d]
Moderate or severe depression [b]	179 (22)	66 (17)	113 (26)	0.002
Moderate or severe anxiety [b]	243 (30)	98 (26)	145 (34)	0.011
Type of OAT [c]				
Methadone	662 (81)	316 (81)	346 (80)	0.722
Buprenorphine/naloxone	85 (10)	41 (11)	44 (10)	0.909
Slow-release oral morphine	72 (9)	20 (5)	52 (12)	< 0.001
Injectable OAT (diacetylmorphine, hydromorphone)	63 (8)	33 (9)	30 (7)	0.433
Other/Unknown	6 (1)	4 (1)	2 (1)	0.589[e]
UDT results[a]				
Positive for morphine (opiates)	503 (61)	136 (35)	367 (85)	< 0.001
Positive for EDDP (methadone)	607 (74)	307 (79)	300 (70)	0.002
Positive for buprenorphine	57 (7)	33 (9)	24 (6)	0.131
Positive for oxycodone	15 (2)	11 (3)	24 (6)	0.065
Positive for cocaine	439 (54)	185 (48)	254 (59)	0.002
Positive for amphetamine	366 (45)	97 (25)	269 (62)	< 0.001
Positive for benzodiazepine	152 (19)	73 (19)	79 (18)	0.858
Structural-level factors [c]				
Homelessness	172 (21)	47 (12)	125 (30)	< 0.001
Incarceration	59 (7)	14 (3)	45 (10)	< 0.001

UDT, urine drug test. THC, tetrahydrocannabinol. BPI, Brief Pain Inventory. OAT, opioid agonist therapy. EDDP, 2-Ethylidine-1, 5-dimethyl-3, 3-diphenylpyrrolidine.

[a] Refers to the day of the interview.
[b] Refers to the 7 days prior to the interview.
[c] Refers to the 6-month period prior to the interview.
[d] Wilcoxon rank sum test.
[e] Fisher's exact test.

using different modeling approaches. First, we employed an approach described by Maldonado et al. (Maldonado and Greenland, 1993). Starting with a full model including the primary explanatory variable (i.e., recent cannabis use) and covariates associated with the outcome in bivariable analyses at $p < 0.10$, we constructed reduced models in a stepwise manner, removing the variable that resulted in the smallest relative change for the fentanyl exposure coefficient. We continued this process until the minimum coefficient change exceeds 5 %. Remaining covariates were considered potential confounders. Second, we fit a multivariable model including all covariates significant at $p < 0.05$ in bivariable analyses.

Given the limited availability of slow-release oral morphine and injectable OAT in other settings, we conducted a sub-analysis, where we investigated the impacts of recent cannabis use on fentanyl exposure restricted to participants on methadone- or buprenorphine/naloxone-based OAT. We also performed a sub-analysis in which we restricted the analytic sample to periods with positive UDT for methadone or buprenorphine. A final sub-analysis employed self-report data on cannabis use in the previous 180 days ($\geq$ daily vs. $<$ daily).

All analyses were conducted in R (Version 3.5.2, R Foundation for Statistical Computing, Vienna, Austria), and all p-values are two-sided.

3. Results

Between December 2016 and November 2018, 819 participants reported being enrolled in OAT and completed a UDT, contributing a total of 1989 observations, or 995 person-years of follow-up. Characteristics of the study sample at the beginning of the study period are summarized in Table 1. The median age was 48 years (interquartile range [IQR] 38–55), over half self-identified as men (467, 57.0 %) and white (489, 59.7 %), and approximately a third of participants were living with HIV (283, 34.6 %). The majority of participants were enrolled in methadone-based OAT programs (662, 80.8 %), followed by buprenorphine/naloxone-based OAT (85, 10.4 %). Use of illicit substances was prevalent, as demonstrated by high rates of UDT positivity for fentanyl (431, 52.6 %) and stimulants (439, 53.6 % for cocaine and 366, 44.7 % for methamphetamine.) Also, as shown in Table 1, at baseline, cannabis users (i.e., participants with UDT positive for THC) were more likely to be men and using benzodiazepines, and less likely to be using opioids, as per UDT results.

As indicated in Table 2, in unadjusted analysis, recent use of cannabis was associated with reduced odds of recent exposure to fentanyl (Prevalence Ratio = 0.90, 95 % Confidence Interval [CI]: 0.83–0.99). Other factors negatively associated with fentanyl exposure in bivariable analyses included: age, and UDT positive for EDDP (methadone) and buprenorphine. Conversely, moderate/severe depression, slow-release oral morphine-based OAT, recent homelessness, and recent use of opiates or stimulants (as indicated by positive UDT for these substances) were positively associated with recent exposure to fentanyl. The negative association between cannabis use and fentanyl exposure remained in the multivariable longitudinal model, with cannabis users in OAT having significantly lower prevalence of fentanyl exposure compared to non-cannabis users (Adjusted Prevalence Ratio [APR] = 0.91, 95 % CI: 0.83 – 0.99) in a model adjusted for all other explanatory covariates.

Our sub-analyses employing different multivariable modeling

Table 2
Unadjusted and adjusted generalized estimating equation analyses of the association between recent exposure to cannabis and recent exposure to fentanyl among people on OAT, Vancouver, Canada (2016–2018).

	Unadjusted		Adjusted	
	Prevalence Ratio (95 % CI)	*p* - value	Prevalence Ratio (95 % CI)	*p* - value
Primary variable of interest				
UDT positive for THC[a]	0.90 (0.89–0.99)	0.023	0.91 (0.83–0.99)	0.032
Socio-demographics				
Age (per year older)	0.98 (0.97–0.98)	< 0.001	0.99 (0.98–0.99)	< 0.001
Male gender	0.93 (0.83–1.04)	0.195	1.05 (0.96–1.14)	0.274
White race	0.92 (0.83–1.02)	0.113	0.99 (0.91–1.07)	0.736
≥High school education	1.01 (0.91–1.11)	0.913	1.07 (0.99–1.16)	0.093
Comorbidities				
HIV positive	0.92 (0.83–1.03)	0.152	0.97 (0.89–1.06)	0.483
BPI severity scale[a,b]	1.00 (0.99–1.01)	0.881	0.99 (0.97–1.01)	0.287
BPI interference scale [a]	1.01 (1.00–1.02)	0.209	1.01 (0.99–1.02)	0.484
Moderate or severe depression [b]	1.09 (1.01–1.19)	0.036	0.97 (0.89–1.06)	0.488
Moderate or severe anxiety [b]	1.07 (0.99–1.15)	0.107	1.01 (0.93–1.10)	0.836
Type of OAT				
On methadone [c]	0.97 (0.87–1.07)	0.505	1.08 (0.95–1.23)	0.231
On buprenorphine/naloxone [c]	0.86 (0.72–1.03)	0.098	0.93 (0.76–1.14)	0.511
On slow-release oral morphine [c]	1.30 (1.18–1.42)	< 0.001	1.15 (1.04–1.28)	0.008
On injectable OAT (diacetylmorphine, hydromorphone) [c]	1.04 (0.88–1.23)	0.635	0.89 (0.76–1.05)	0.180
On another/ unknown OAT [c]	1.04 (0.75–1.46)	0.801	1.01 (0.68–1.49)	0.971
UDT results[a]				
Positive for morphine (opiates)	2.07 (1.85–2.32)	< 0.001	1.87 (1.65–2.10)	< 0.001
Positive for EDDP (methadone)	0.89 (0.81–0.98)	0.016	0.97 (0.87–1.08)	0.576
Positive for buprenorphine	0.76 (0.60–0.97)	0.027	0.99 (0.76–1.29)	0.927
Positive for oxycodone	0.83 (0.63–1.10)	0.193	0.75 (0.55–1.02)	0.071
Positive for cocaine	1.19 (1.09–1.29)	< 0.001	1.18 (1.10–1.28)	< 0.001
Positive for amphetamine	1.68 (1.53–1.84)	< 0.001	1.40 (1.28–1.53)	< 0.001
Positive for benzodiazepine	1.04 (0.95–1.14)	0.388	1.06 (0.96–1.16)	0.251
Social-structural factors [c]				
Homelessness	1.24 (1.12–1.37)	< 0.001	1.02 (0.94–1.10)	0.713
Incarceration	1.10 (0.94–1.29)	0.152	0.97 (0.85–1.10)	0.601

UDT, urine drug test. THC, tetrahydrocannabinol. BPI, Brief Pain Inventory. OAT, opioid agonist therapy. EDDP, 2-Ethylidine-1, 5-dimethyl-3, 3-diphenylpyrrolidine.
[a] Refers to the day of the interview.
[b] Refers to the 7 days prior to the interview.
[c] Refers to the 6-month period prior to the interview.

strategies yielded similar results. Specifically, in a multivariable model fit using the backwards-selection approach, the APR for cannabis use was 0.92 (95 % CI: 0.84 – 0.99) after adjustment for UDT morphine and UDT amphetamine results and HIV status. In the multivariable model including all covariates significant in bivariable analyses, the APR for cannabis was 0.91 (0.84–0.99).

Our sub-analysis restricted to 733 participants on only methadone- or buprenorphine/naloxone-based OAT, who contributed 1739 observations, yielded a similar result (APR = 0.91, 95 % CI: 0.83–0.99) in a multivariable model adjusted for all other explanatory variables. When the analytic sample was constructed using positive UDT for methadone or buprenorphine, the adjusted estimate for cannabis use (including all explanatory variables except for urine drug test results for methadone and buprenorphine) was largely unchanged from the primary analysis: APR = 0.89, 95 % CI: 0.81–0.98. In the final sub-analysis employing a self-reported measure of cannabis use in the previous 180 days, there was no significant relationship with fentanyl exposure (APR = 1.10, 95 % CI: 0.97–1.24).

4. Discussion

In the present study, we found that among over 800 study participants on OAT in Vancouver, Canada, between 2016–2018, use of cannabis was associated with significantly lower risk of exposure to fentanyl. This negative association persisted after adjustment for a broad range of covariates, including concurrent use of other illicit substances such as opioids and stimulants. Although we cannot infer causality from our findings, they are broadly consistent with exploratory qualitative research from our setting and others documenting the intentional use of cannabis as a strategy to reduce the use of illicit opioids, address the harms of other substances, and treat common comorbidities, including chronic pain (Boyd et al., 2017; Labigalini et al., 1999; Lau et al., 2015; Valleriani et al., 2019).

The impacts of cannabis use on illicit opioid use and related harms remains an area of active research. Observational research in specific populations—including senior high-school students in the United States (Palamar et al., 2018) and marginalized people who use drugs in our study setting (Reddon et al., 2020)—have reported lower levels of illicit opioid use associated with high-frequency cannabis use. Pre-clinical studies have described important interactions between the opioid and endocannabinoid receptor systems (Befort, 2015), and two preliminary experimental studies among humans have demonstrated changes in opioid-related outcomes following controlled administration of cannabinoids (Cooper et al., 2018; Hurd et al., 2019). However, findings from most studies to date are inconclusive. Specifically, systematic reviews of observational research conducted among medicinal cannabis patients (mostly chronic pain patients) found mixed evidence on the impacts of cannabis use on prescription opioid needs and outcomes (Campbell et al., 2018). Likewise, research conducted in the context of methadone-based OAT also provides conflicting evidence, with the majority of studies showing no effect of cannabis use on illicit opioid consumption among OAT clients (McBrien et al., 2019). Importantly, as authors from these reviews highlight, comparisons across studies are problematic given important differences in how cannabis and opioid use was measured (e.g., self-report versus UDT, baseline versus time-updated), study populations and settings. Drawing definite

conclusions on the potential of cannabinoids to reduce opioid-related harms is further complicated by the overall low quality of evidence of available studies and lack of information on details of cannabis use (e.g., types, potencies, dose/dosages, and routes of administration).

In the context of this limited and conflicting evidence, our study adds to the literature by demonstrating for the first time a negative longitudinal association between cannabis use and recent fentanyl exposure among people on OAT recruited from community settings during the current overdose crisis. These results are in line with a previous study from California indicating a lower frequency of illicit opioid use among people who inject drugs and also use cannabis (Kral et al., 2015). The present analysis also extends previous research from our setting which found a significantly lower likelihood of fentanyl exposure linked to cannabis use among people who inject drugs (Ahamad et al., 2015). In both of these studies, it is noteworthy that no other substance was associated with reduced risk of illicit opioid use. More recently, we have documented that study participants initiating OAT were more likely to be retained in treatment at six months if they were concomitantly using cannabis on a daily basis (Socias et al., 2018). Taken together, these findings would suggest that some people who use drugs (including those on OAT) may be using cannabis as a harm reduction or self-medication strategy to reduce their use of illicit opioids by managing cravings, withdrawal symptoms, or other common comorbidities in this population, including pain, anxiety, or insomnia (Lake et al., 2019; Wenger et al., 2014). This has been documented in a number of exploratory qualitative analyses among individuals from our study setting, in which some participants reported the intentional use of cannabis to control the use of other drugs and mitigate their risks, treat comorbidities like chronic pain, and address opioid withdrawal (Boyd et al., 2017; Labigalini et al., 1999; Lau et al., 2015; Valleriani et al., 2019). As such, as this body of research moves forward, it will be important to consider accessibility and affordability of legal medical and non-medical cannabis for structurally marginalized populations, especially as cannabis is typically not covered by public or private medical insurers.

We emphasize that we cannot exclude non-causal explanations for these findings. For example, our findings might be the result of cannabis-using OAT clients having a lower latent risk of fentanyl exposure. However, the negative association between cannabis use and fentanyl exposure remained after adjusting for a range of relevant confounders, including socio-demographic and substance use characteristics. In light of the unanswered questions about the impacts of cannabis use among people on OAT—as well as the need to develop new strategies and approaches to lower rates of relapse into illicit opioid use in the context of the ongoing opioid crisis—findings from this and past research underscore the urgent need for experimental research to better understand the potential benefits and possible harms of using cannabinoids as adjunct therapy to OAT. Research using the controlled administration of specific cannabinoids would build on the findings from a recent placebo-controlled and blinded trial that found that cannabidiol (CBD), an important phytocannabinoid, significantly reduced visual cue-induced cravings among a small group of abstinent individuals with OUD (Hurd et al., 2019).

A number of limitations should be considered when interpreting results from this analysis. First, our study sample was not randomly selected. Most of our participants were recruited from areas with high rates of poverty, homelessness and substance use and, most importantly, a setting with a community-wide overdose crisis sparked by the widespread contamination of the illicit drug supply with fentanyl. Therefore, our findings may not be generalizable to other populations of OAT clients, particularly those with less social/structural marginalization. Second, this study cannot prove a causal relationship between cannabis use and reduced risk of fentanyl exposure. Specifically, given the observational nature of our study, and despite the use of multivariable techniques to account for possible confounders, we cannot rule out the possibility of unmeasured confounding impacting our results. In addition, we did not collect data on type of cannabis used (including combinations with CBD), dose, frequency of use, mode of administration or reasons for use. In future research we will seek to better characterize potential differential impacts of these aspects of cannabis use, as this will be critical to inform potential therapeutic uses of cannabinoids in the context of OAT. Third, both our main explanatory variable and outcome relied on results from UDT. While this is a strength as it allowed us to confirm recent (i.e., 1–3 days) use or exposure to fentanyl (particularly as individuals may not know that they are being exposed to fentanyl through contaminated substances), THC may be detected in urine for up to 30 days after last use for chronic heavy cannabis users (Moeller et al., 2017), making it difficult to confirm recent use in these cases. UDT have other limitations, including false positives due to cross-reactivity with other substances or false negatives when the concentration of the substance being tested is below the cut-off limit, as well as the inability to detect fentanyl analogues (Moeller et al., 2017). They are also unable to detect other opioid novel psychoactive substances. Finally, while self-reporting data to assess other variables may have influenced by reporting bias, reports by people who use drugs have generally been shown to be valid (Darke, 1998).

In conclusion, we found that among more than 800 participants on OAT in Vancouver, Canada, use of cannabis was longitudinally associated with a substantially lower risk of being exposed to fentanyl. Given the magnitude of the overdose crisis in the U.S. and Canada and the substantial contributions of fentanyl to the burden of overdose morbidity and mortality, findings from this study support the experimental evaluation of cannabinoids as a potential adjunct therapy to OAT to improve clinical outcomes, particularly to reduce the risk of relapse to illicit opioid use (i.e., fentanyl) and associated risk of overdose and death.

Contributors

- M-JM and ES conceived of the study, determined the objectives and hypotheses, and prepared the analytic plan;
- JCC performed all statistical analyses;
- ES drafted the manuscript, incorporated revisions from co-authors, and prepared the final version for review and submission;
- EW, TK, KH and M-JM conceived of or manage the study's parent prospective cohorts;
- EW, SL, KH, and JV provided input into the study's methods, interpretation of results, or the existing literature on cannabis and opioid use;
- All authors reviewed the draft manuscript, provided meaningful input, and approved the final article for submission

Declaration of Competing Interest

JV was appointed as Director of Global Patient Advocacy for Canopy Growth in January 2020, after the completion of this manuscript. She did not contribute to the study's methodological design or data analysis. M-JM declares no competing interests, e.g., employment, consultancies, stock ownership, honouraria, paid expert testimony, patents, grants or other funding. Other authors declare no competing interests.

Acknowledgements

The authors thank the study participants for their contributions to the research, as well as current and past researchers and staff. This work was supported by the US National Institute on Drug Abuse (NIDA) (U01-DA038886 and U01-DA021525). MES is supported by a Michael Smith Foundation for Health Research (MSFHR)/St Paul's Foundation Scholar Award. KH is supported by a CIHR New Investigator and MSFHR Scholar Awards, and the St. Paul's Foundation. SL is supported by doctoral scholarships from CIHR and the Pierre Elliott Trudeau Foundation. M-JM is supported by NIDA (U01-DA021525), a CIHR New Investigator and MSFHR Scholar Awards. M-JM is the Canopy Growth professor of

cannabis science at the University of British Columbia, a position created by unstructured gifts to the University from Canopy Growth, a licensed producer of cannabis, and the Government of British Columbia's Ministry of Mental Health and Addictions. The University of British Columbia has also received unstructured funding from NG Biomed, Ltd. to support M-JM.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.drugalcdep.2020.108420.

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