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Crystal methamphetamine use and methadone maintenance treatment dissatisfaction: A prospective cohort study in Vancouver, Canada

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Abstract

Background: Patient satisfaction is key to the success of methadone maintenance treatment (MMT), and yet how MMT satisfaction is affected by the increasingly common use of crystal methamphetamine among people receiving opioid treatment remains poorly understood. We aimed to assess the association between crystal methamphetamine use and MMT dissatisfaction.

Methods: We employed generalized estimating equations to examine the relationship between crystal methamphetamine use and MMT dissatisfaction among patients receiving MMT within two prospective cohorts in Vancouver, Canada, between December 2016 and March 2020.

Results: Of the 836 participants receiving MMT, the median age was 47 years, and 55.3% self-identified as male at baseline. In a multivariable model, those reporting more than weekly crystal methamphetamine use were more likely to report MMT dissatisfaction (Odds ratio: 1.40, 95% confidence interval: 1.05–1.86) compared to those reporting less than monthly crystal methamphetamine use.

Conclusions: Among our sample of people receiving MMT, we noted a positive association of frequent crystal methamphetamine use with MMT dissatisfaction. Our study suggests a need for novel strategies to better understand and address frequent methamphetamine use among those receiving MMT, particularly given recent shifts in substance use patterns involving the rising co-use of methamphetamines and opioids.

Word count: 197

1. Introduction

In the context of the ongoing overdose crisis in the United States (US) and Canada, opioid-related overdose remains a leading cause of accidental death (NIDA, 2021; Government of Canada, 2021), driven in large part by illicitly manufactured fentanyl and its analogues in the unregulated drug supply (Coroners Service, 2017). The province of British Columbia (BC), Canada, has experienced an unprecedented number of overdose deaths in recent years and the provincial government declared a public health emergency in April 2016 (BC Centre for Disease Control, 2017).

Opioid agonist therapy (OAT) remains the first-line treatment for opioid use disorder (OUD) and research has shown it to be superior to withdrawal management in treatment retention and reduction of illicit opioid use, morbidity, and all-cause mortality (Bahji et al., 2019; National Institute on Drug Abuse, 2018). The provincial OUD guidelines in BC recommend that medically supervised OAT, including buprenorphine-naloxone or methadone, should be offered to patients with OUD in the absence of contraindications (Bruneau et al., 2018). Methadone maintenance treatment (MMT) has historically been the standard of care for OUD in BC and is still considered first-line treatment in patients using high daily doses of opioids or with a history of severe withdrawal symptoms (Lu, 2020). In 2019, nearly 70% of individuals on OAT were on MMT in BC (British Columbia Centre for Disease Control, 2021).

Research has shown that treatment satisfaction is key to the success of MMT, including promoting retention in MMT and reducing unregulated opioid use (Kelly et al., 2010; Perreault et al., 2010). Understanding the factors that promote or undermine patient satisfaction is critical to optimizing OAT outcomes. Past research has identified stigma, side effects, demanding programmatic requirements, and unmet social and other medical needs as being associated with

lower satisfaction with MMT (Alcaraz et al., 2017; Muller et al., 2018). Additionally, studies have suggested that patients may use methamphetamine to counter the sedating effects of methadone (McNeil et al., 2020). Given the noted rising prevalence of methamphetamine use among people receiving opioid treatment (Ellis et al., 2018; Fischer et al., 2021), that the use of methamphetamine may be associated with reduced retention in MMT is concerning (O'Connor et al., 2020). However, an understanding of the relationship between methamphetamine use and MMT satisfaction is lacking.

Our study aims to evaluate the relationship between crystal methamphetamine (“crystal meth”) use and MMT satisfaction. We hypothesize that patients reporting crystal meth use will be more likely to report MMT dissatisfaction. As such, we aim to contribute to a better understanding of the challenges presented by rising crystal meth use among patients receiving opioid treatment and thereby inform integrated treatment strategies for people who co-use methamphetamines and opioids.

2. Methods

2.1 Study sample

The Vancouver Injection Drug Users Study (VIDUS) and the AIDS Care Cohort to evaluate Exposure to Survival Services (ACCESS) are two open prospective cohort studies of adults who use unregulated drugs in Vancouver, Canada. Details of these cohorts have been described in previous studies (Kerr et al., 2005; Wood et al., 2004). In brief, participants of VIDUS and ACCESS are recruited through self-referral, word of mouth, and street outreach primarily in the Downtown Eastside neighborhood of Vancouver, which is characterized by high rates of unregulated drug use (Friedel & Staak, 1993). VIDUS enrolls HIV-negative adults who report

having injected unregulated drugs in the month preceding enrollment and ACCESS enrolls HIV-positive individuals who report having used unregulated drugs other than or in addition to cannabis in the month preceding enrollment. Once enrolled, at baseline and semi-annually thereafter, participants complete an interviewer-administered questionnaire obtaining information on socio-demographic characteristics, drug use patterns, risk behaviors, and health care utilization. The study instruments and follow-up procedures for these cohorts are harmonized to allow for combined analyses. Participants receive a \$40 (CDN) honorarium for each study visit. All eligible participants provided written informed consent. The studies have been approved by the University of British Columbia/Providence Health Care Research Ethics Board.

For the current study, we restricted our analysis to participants who completed a study visit between December 2016 and March 2020, given that the OAT satisfaction question was added to the questionnaire as of December 2016. We further restricted our sample to those visits in which participants reported to have received MMT in response to the question “in the last 6 months, have you received any medications (such as Methadose or Suboxone) for the treatment of your alcohol or drug use?”

2.2 Study variables

The study outcome was MMT dissatisfaction, measured by asking “how satisfied were you with the medication treatment you received?” A five-point Likert scale was dichotomized as “very unsatisfied” or “unsatisfied” versus “neutral” or “satisfied” or “very satisfied”. The main exposure was crystal meth use frequency by any route, categorized as “none to less than monthly use”, “monthly to weekly use”, and “more than weekly use”. Based on existing research, we considered explanatory variables that could be associated with crystal meth use frequency or

MMT satisfaction (Alcaraz et al., 2017; Damon et al., 2019; Lake et al., 2021; Mackay et al., 2021; Muller et al., 2018). These variables included: age, self-identified gender (male vs. non-male), sexual orientation (heterosexual vs. other), self-reported ethnicity/ancestry (white vs. Indigenous vs. other), cohort designation (VIDUS vs. ACCESS), unstable housing (hotel/shelter/recovery house/street/other vs. apartment/house), Downtown Eastside residence, drug-dealing involvement, incarceration, and MMT dose (>100 mg/day vs. ≤100mg/day). Substance-use variables other than crystal meth use include crack or cocaine, cannabis, alcohol, and unregulated opioids use (i.e., heroin or fentanyl), and were categorized as “none to less than monthly use”, “monthly to weekly use”, and “more than weekly use”. As patients who were dissatisfied with MMT would likely engage in unregulated opioid use, we used unregulated opioid use frequency collected during the visit immediately preceding the ascertainment of MMT dissatisfaction. In addition, we also controlled for new initiates of MMT, defined as a participant reporting not being on MMT in an immediately preceding study visit. All variables except for ethnicity were time-varying and dichotomized as yes vs. no unless otherwise noted.

2.3 Statistical analysis

First, we compared the baseline sample characteristics stratified by ever being dissatisfied with MMT at any point during the study period, using the Pearson's χ^2 test for categorical variables and the Wilcoxon Rank Sum test for continuous variables. Second, we conducted univariable and multivariable GEE models to study the relationship between crystal meth use frequency and MMT dissatisfaction. All explanatory variables of interest were included in the multivariable GEE model. The amount of missing data was minimal (< 1% for each variable and overall), and thus the study removed missing data from the multivariable model. All statistical tests were two-

sided and considered statistically significant at $p < 0.05$. The study team used SAS version 9.4 to conduct all analyses (SAS Institute, Cary, North Carolina, United States).

3. Results

Between December 2016 and March 2020, 836 participants who reported receiving MMT in the previous six months were included in this study. The median follow-up time per individual was 2.2 years (1st to 3rd quartile [Q1-Q3] = 1.1–3.1). During the study follow-up, our participants contributed a median of 3 visits (Q1-Q3 = 2–6), resulting in 3009 visits included in this analysis.

Table 1 presents the baseline characteristics of all participants stratified by MMT dissatisfaction. During our study period, more than half (50.7%) of participants reported ever being dissatisfied with MMT. As shown, 555 (66.4%) participants were from VIDUS (i.e., HIV negative) and 281 (33.6%) were from ACCESS (i.e., HIV positive). Among all participants, the median age at baseline was 47 years (Q1-Q3 = 37–54), 462 (55.3%) self-identified as being male; 479 (57.8%) self-identified as white and 316 (38.1%) identified as being of Indigenous ancestry. At study baseline, 170 (20.3%) participants reported daily use of crystal meth and 327 (39.1%) reported daily use of unregulated opioids, 129 (15.4%) of whom reported daily use of both crystal meth and unregulated opioids.

We present the results of the univariable and multivariable GEE analyses in Table 2. The univariable GEE model shows that compared to those reporting less than monthly crystal meth use, patients reporting more than weekly crystal meth use were more likely to report MMT dissatisfaction (odds ratio: 1.34, 95% confidence interval [CI]: 1.07–1.67). After adjusting for confounders and other predictors, the multivariable model shows that patients reporting more

than weekly crystal meth use were more likely to report MMT dissatisfaction (adjusted odds ratio: 1.40, 95% CI: 1.05–1.86) compared to those reporting less than monthly crystal meth use. The odds of reporting MMT dissatisfaction between patients reporting monthly to weekly crystal meth use were not significantly different from those reporting less than monthly crystal meth use.

4. Discussion

Using data from two large prospective cohort studies, we found a positive association between frequent crystal meth use and MMT dissatisfaction among individuals receiving MMT between late 2016 to early 2020 in Vancouver, Canada. Specifically we found that, compared to patients who reported less than monthly crystal meth use, those who reported more than weekly crystal meth use were significantly more likely to report MMT dissatisfaction, and those who reported monthly to weekly crystal meth use were similarly likely to report MMT dissatisfaction.

In our study setting, the increasing prevalence of crystal meth use, especially in combination with opioids, poses challenges for MMT (Mackay et al., 2021; O'Connor et al., 2020). In a qualitative study published in 2020, McNeil et al. suggest that some patients receiving MMT use crystal meth to counter the sedating effects of methadone (McNeil et al., 2020). Additionally, crystal meth use could be a marker of ongoing unregulated opioid use among patients receiving MMT. Especially, as potent synthetic opioids have become increasingly available in our local unregulated drug supply, crystal meth may be used to prevent over-sedation caused by potent synthetic opioids (e.g., fentanyl) (BC Coroners Service, 2021; Ellis et al., 2018). In turn, crystal meth use could make it more challenging to stabilize some patients on MMT. O'Connor et al.'s 2020 systematic review summarized that three of five studies conducted in the United States and Canada show a significant association between methamphetamine use and reduced methadone

retention (O'Connor et al., 2020). Furthermore, a recently published analysis conducted using the same cohorts as our analysis noted a dose-dependent relationship between the frequency of methamphetamine use and methadone discontinuation (Mackay et al., 2021). Our study adds to the existing research to help explain the noted relationship between frequent crystal meth use and reduced methadone retention by suggesting a relationship between frequency of crystal meth use and MMT dissatisfaction.

Our study provided a better understanding of crystal meth use among patients receiving MMT, which might allow care providers to more accurately predict the treatment effects of MMT. The positive relationship between frequent crystal meth use and MMT dissatisfaction points to the need for regular and consistent assessment during MMT visits to improve MMT success overall, including treatment satisfaction and retention. For example, care providers could carefully explore patients' crystal meth use frequency. If patients report more-than-weekly crystal meth use, providers should assess MMT treatment satisfaction and should explore other opioid treatment options. Moreover, in addition to the urgent need for the development of pharmacologic treatments to treat methamphetamine dependence, a timely response is also needed to counter the rapidly rising methamphetamine use patterns among patients receiving opioid treatment (Ellis et al., 2018). In a systematic review published in 2020, Brown and DeFulio summarized the broad benefits of contingency management intervention programs that offer treatment for methamphetamine use disorder (Brown & DeFulio, 2020). Care providers could consider incorporating contingency management programs into regular OAT visits for patients who concurrently use methamphetamines and opioids (Morley et al., 2017). However, given the limited durability of the benefits of such interventions (Morley et al., 2017), work needs to continue to focus on identifying novel strategies to address crystal meth use.

Our study has several limitations. First, the participants in both VIDUS and ACCESS were recruited with nonrandom sampling, and our study sample is characterized by a high proportion of participants living in the Downtown Eastside of Vancouver, a unique neighborhood with high rates of polysubstance use (Friedel & Staak, 1993). Therefore, the generalizability of our findings could be limited. Second, self-reported data used in this study could be subject to reporting biases. However, prior research has suggested that self-reported data were generally accurate among drug-using populations (Darke, 1998). Third, we could not account for MMT adherence or differentiate reasons for MMT dissatisfaction due to data limitations. However, considering the complex nature of MMT engagement, the broad nature of our sample could better speak to the issues of MMT in practice. Future research should build on richer quantitative data or qualitative interviews to understand meaningful factors causing MMT dissatisfaction. Last, we cannot infer causation between crystal meth use and MMT satisfaction in this observational study due to the concerns of unmeasured confounding and reverse causation. The study could not establish temporality as patients could have been dissatisfied with MMT before they start to use crystal meth.

In conclusion, our study noted the potential challenges to treatment satisfaction presented by rising crystal meth use among people receiving MMT. In response to the recent shifts in substance use patterns where methamphetamine-opioid co-use is rapidly rising, our study highlights the need for improved care options for patients engaging in frequent crystal meth use while receiving OAT. Such efforts have the potential to help increase MMT satisfaction. Future research needs to depict the direct and indirect pathways between crystal meth use and MMT success to better inform effective integrated strategies targeting patients who use crystal meth while receiving MMT.

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Table 1. Baseline sample characteristics stratified by ever reported treatment dissatisfaction during the study period among participants receiving methadone maintenance treatment in Vancouver, Canada (N = 836).

Variables	Treatment Dissatisfaction			<i>p</i> -value
	Total (N = 836) N (%)	No (N = 412) N (%)	Yes (N = 424) N (%)	
Crystal Meth Use Frequency ^a				
Less than monthly use	497 (59.5%)	244 (59.2%)	253 (59.7%)	0.968
Monthly to weekly use	69 (8.3%)	35 (8.5%)	34 (8.0%)	
More than weekly use	270 (32.3%)	133 (32.3%)	137 (32.3%)	
Crack or Cocaine Use Frequency ^a				
Less than monthly use	529 (63.3%)	272 (66.0%)	257 (60.6%)	0.194
Monthly to weekly use	98 (11.7%)	48 (11.7%)	50 (11.8%)	
More than weekly use	209 (25.0%)	92 (22.3%)	117 (27.6%)	
Alcohol Use Frequency ^a				
Less than monthly use	589 (70.5%)	316 (75.2%)	279 (65.8%)	0.004
Monthly to weekly use	133 (15.9%)	49 (11.9%)	84 (19.8%)	
More than weekly use	114 (13.6%)	53 (12.9%)	61 (14.4%)	
Cannabis Use Frequency ^a				
Less than monthly use	326 (39.0%)	162 (39.3%)	164 (38.7%)	0.177
Monthly to weekly use	474 (56.7%)	227 (55.1%)	247 (58.3%)	
More than weekly use	36 (4.3%)	23 (5.6%)	13 (3.1%)	
Unregulated Opioid Use Frequency ^a				
Less than monthly use	308 (36.8%)	162 (39.3%)	146 (34.4%)	0.199
Monthly to weekly use	104 (12.4%)	54 (13.1%)	50 (11.8%)	
More than weekly use	424 (50.7%)	196 (47.6%)	228 (53.8%)	

^avariables refers to the last six months prior to the interview date.

Table 1 continued. Baseline sample characteristics stratified by ever reported treatment dissatisfaction during the study period among participants receiving methadone maintenance treatment in Vancouver, Canada (N = 836).

Variables	Treatment Dissatisfaction			<i>p</i> -value
	Total (N = 836) N (%)	No (N = 412) N (%)	Yes (N = 424) N (%)	
Age (Median (Q1-Q3))	47 (37-54)	45 (35-53)	48 (39-55)	<.001
Cohort				
ACCESS	281 (33.6%)	133 (32.3%)	148 (34.9%)	0.422
VIDUS	555 (66.4%)	279 (67.7%)	276 (65.1%)	
Ethnicity/Ancestry				
White	479 (57.8%)	230 (56.5%)	249 (59.0%)	0.766
Indigenous	316 (38.1%)	160 (39.5%)	156 (37.0%)	
Other person of color	34 (4.1%)	17 (4.2%)	17 (4.0%)	
Male gender	462 (55.3%)	229 (55.5%)	233 (55.0%)	0.855
Sexual Orientation - Heterosexual	130 (15.6%)	64 (15.5%)	66 (15.6%)	0.990
Unstable Housing ^a	563 (67.4%)	283 (68.9%)	280 (66.0%)	0.385
Living in Downtown Eastside ^a	619 (74.2%)	305 (74.0%)	314 (74.4%)	0.901
Drug-dealing ^a	73 (8.7%)	41 (10.0%)	32 (7.6%)	0.218
Incarceration ^a	169 (20.2%)	84 (20.4%)	85 (20.1%)	0.902
New Methadone Initiates	125 (22.3%)	104 (25.3%)	82 (19.4%)	<.001
High Methadone Dose ^a	225 (25.7%)	131 (38.0%)	125 (33.5%)	0.213

^avariables refers to the last six months prior to the interview date.

Table 2. Univariable and multivariable GEE analyses of the relationship between crystal meth use frequency and treatment dissatisfaction among participants receiving methadone maintenance treatment in Vancouver, Canada. (N = 3009).

	Treatment Dissatisfaction	
	OR ^c (95% CI)	aOR ^c (95% CI)
Crystal Meth Use Frequency ^a (Ref: Less than monthly use)		
Monthly to weekly use	1.16 (0.85 - 1.58)	0.99 (0.70 - 1.41)
More than weekly use	1.34 (1.07 - 1.67)	1.40 (1.05 - 1.86)
Crack or Cocaine Use Frequency ^a (Ref: Less than monthly use)		
Monthly to weekly use	1.05 (0.81 - 1.36)	1.14 (0.86 - 1.52)
More than weekly use	0.91 (0.71 - 1.17)	0.95 (0.71 - 1.27)
Alcohol Use Frequency ^a (Ref: Less than monthly use)		
Monthly to weekly use	1.32 (1.04 - 1.68)	1.23 (0.95 - 1.61)
More than weekly use	1.28 (0.99 - 1.65)	1.09 (0.83 - 1.45)
Cannabis Use Frequency ^a (Ref: Less than monthly use)		
Monthly to weekly use	1.20 (0.81 - 1.22)	1.07 (0.85 - 1.33)
More than weekly use	0.91 (0.70 - 1.18)	1.02 (0.76 - 1.38)
Unregulated Opioid Use Frequency ^{a,b} (Ref: Less than monthly use)		
Monthly to weekly use	1.30 (0.96 - 1.77)	1.30 (0.93 - 1.83)
More than weekly use	1.50 (1.18 - 1.92)	1.58 (1.20 - 2.10)
Age (per year increase)	1.00 (0.99 - 1.01)	1.02 (1.01 - 1.04)
Calendar Year (per year increase)	0.86 (0.80 - 0.93)	0.81 (0.72 - 0.90)
Cohort (VIDUS vs. ACCESS)	1.09 (0.86 - 1.38)	1.03 (0.79 - 1.35)
Ethnicity/Ancestry (White vs. Other)	1.12 (0.89 - 1.41)	1.14 (0.87 - 1.49)
Gender (Male vs. Non-male)	1.08 (0.86 - 1.35)	1.06 (0.82 - 1.37)
Sexual Orientation (Other vs. Heterosexual)	1.45 (1.11 - 1.88)	1.61 (1.20 - 2.15)
Unstable Housing ^a	1.09 (0.89 - 1.34)	1.20 (0.93 - 1.54)
Living in Downtown Eastside ^a	0.76 (0.62 - 0.94)	0.61 (0.46 - 0.79)
Drug-dealing ^a	1.29 (1.02 - 1.63)	1.24 (0.94 - 1.63)
Incarceration ^a	1.18 (0.79 - 1.76)	1.08 (0.69 - 1.70)
New Methadone Initiates	1.04 (0.77 - 1.40)	1.06 (0.71 - 1.58)
High Methadone Dose ^a	0.81 (0.65 - 1.00)	0.79 (0.64 - 0.99)

OR: odds ratio; aOR: adjusted odds ratio; CI: confidence interval.

^avariables refer to the last six months prior to the interview date.

^bvariable collected on the lagged visit of the treatment dissatisfaction outcome.

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Conflict of Interest

MJM's institution has received an unstructured gift from NG Biomed, Ltd., to support his research. MJM 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. Funding sources had no role in study design; collection, analysis, and interpretation of data; writing the report; and the decision to submit the report for publication. All authors declare no conflict of interest.

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Journal Pre-proof

Highlights

- The increasing crystal meth use poses challenges for methadone maintenance treatment;
- Frequent crystal meth use is associated with increased methadone dissatisfaction;
- Improved care options are needed for patients engaging in frequent crystal meth use.

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