



Published in final edited form as:

J Subst Abuse Treat. 2018 November ; 94: 41–46. doi:10.1016/j.jsat.2018.08.009.

FACTORS ASSOCIATED WITH METHADONE MAINTENANCE THERAPY DISCONTINUATION AMONG PEOPLE WHO INJECT DRUGS

Ada Lo^a, Thomas Kerr^{a,b}, Kanna Hayashi^{a,c}, M.-J. Milloy^{a,b}, Ekaterina Nosova^a, Yang Liu^a, and Nadia Fairbairn^{a,b}

^aBritish Columbia Centre on Substance Use, British Columbia Centre for Excellence in HIV/AIDS, St. Paul's Hospital, 608-1081 Burrard Street, Vancouver, BC V6Z 1Y6, Canada

^bDepartment of Medicine, University of British Columbia, St. Paul's Hospital, 608-1081 Burrard Street, Vancouver, BC V6Z 1Y6, Canada

^cFaculty of Health Sciences, Simon Fraser University, 8888 University Drive, Burnaby, BC V5A 1S6, Canada

Abstract

Background—Methadone maintenance therapy (MMT) continues to be a key treatment for opioid use disorder, although premature discontinuation of MMT can increase risk for overdose and other severe harms. We examined sociodemographic characteristics, substance use patterns and social-structural exposures associated with MMT discontinuation among a cohort of people who use drugs (PWUD) in Vancouver, Canada.

Methods—Data were derived from VIDUS and ACCESS, prospective cohorts of PWUD in Vancouver, Canada. The outcome of interest was self-reported discontinuation of MMT within the last six months. Multivariable Generalized Estimating Equations (GEE) were conducted to identify factors independently associated with MMT discontinuation.

Results—Between 2005 and 2015, 1301 PWUD who had accessed MMT were recruited, among whom 288 (22.1%) discontinued MMT at least once during the study period. In multivariable GEE analyses, homelessness (Adjusted Odds Ratio [AOR] = 1.46, 95% Confidence Interval [95% CI]: 1.09–1.95), daily heroin injection (AOR = 5.17, 95% CI: 3.82– 6.99), daily prescription opioid use (injection or non-injection) (AOR = 2.18, 95% CI: 1.30– 3.67), recent incarceration (AOR = 1.46, 95% CI: 1.01–2.12), and not being on any form of income assistance (AOR = 2.14, 95% CI: 1.33– 3.46) were each independently positively associated with MMT discontinuation. Participants with more study visits on methadone (>50% vs. ≤50% of visits) (AOR = 0.63, 95% CI: 0.47–0.85) and those with higher methadone dose (>100 mg vs. ≤60 mg per day) (AOR = 0.44, 95% CI: 0.31– 0.62) were less likely to discontinue MMT.

Discussion and conclusions—Discontinuation of MMT in this urban setting was associated with recent homelessness and incarceration, not accessing social income assistance, as well as daily prescription opioid use and daily heroin injection drug use. These findings underscore a need to reduce potential barriers to MMT retention by providing access to stable housing and preventing treatment interruptions during transitions between community and custodial settings.

Keywords

opioids; people who inject drugs; methadone maintenance therapy; opioid agonist treatment

1. INTRODUCTION

Opioid misuse and addiction are associated with multiple severe health and social harms, including fatal overdose, HIV and hepatitis C infection, and criminal justice involvement (Degenhardt et al., 2017; Rudd, Seth, David, & Scholl, 2016). Opioid agonist treatment, specifically methadone maintenance therapy (MMT), is a cornerstone of treatment for opioid use disorder (OUD) (Stein et al., 2012; World Health Organization, 2015). MMT has been shown to reduce injection drug use, all-cause and overdose mortality, and improve social functioning and quality of life (Salsitz & Wiegand, 2015; Simoens, 2005). Furthermore, MMT supports antiretroviral therapy adherence among HIV-infected individuals (Bach et al., 2015) and has consistently been shown to lower the risk of blood-borne pathogen transmission (Vlahov, Robertson, & Strathdee, 2010). This large body of evidence for MMT has led to its inclusion on the World Health Organization's list of essential medicines since 2005 (WHO Model List of Essential Medicines, 2017).

It is well demonstrated that longer-term (i.e. six months or greater) retention on MMT helps prevent relapse to illicit opioid use (Sees et al., 2000). In addition, it has been shown that individuals who discontinue MMT are at increased risk for fatal overdose (Davoli et al., 2007) and all-cause mortality (Cornish, Macleod, Strang, Vickerman, & Hickman, 2010; Cousins et al., 2016). However, it is estimated that between 46 and 65% of patients who initiate MMT discontinue within the first year and relapse to opioid use (Magura, Nwakeze, & Demsky, 1998; Nosyk, Marsh, Sun, Schechter, & Anis, 2010; Reisinger et al., 2009). Retention on MMT, and prevention of harms associated with relapse to illicit opioid use, therefore remain ongoing challenges.

Though retention on MMT is a critical component of successful treatment for opioid use disorder, factors that predict MMT discontinuation have been less well studied. To help inform strategies that may support MMT retention, we sought to examine the sociodemographic characteristics, substance use patterns, and social-structural exposures associated with MMT discontinuation among people who use drugs (PWUD) in Vancouver, Canada.

2. MATERIAL AND METHODS

2.1. Study participants

Data for this study were collected from two prospective cohorts of PWUD in Vancouver, Canada, the Vancouver Injection Drug Users Study (VIDUS) and the AIDS Care Cohort to Evaluate Exposure to Survival Services (ACCESS). These cohorts have been described previously in detail (Bach et al., 2015; Strathdee, 1998; Wood, 2008). In brief, participants in both cohorts have been recruited since May 1996 through street outreach in the Downtown Eastside, an area with a high prevalence of substance use in Vancouver. VIDUS

is a cohort of HIV-negative PWUD who are eligible for participation in the study if they are at least 18 years old and have injected illicit drugs at least once in the past month prior to study enrollment. ACCESS is a study of HIV-positive adults who have used illicit drugs in the month prior to study enrollment. VIDUS participants who seroconvert to be HIV-positive are transferred to the ACCESS study.

Both studies collect data and conduct follow-ups in a harmonized manner to facilitate combined analyses. At baseline and every six months thereafter, participants answer an interviewer-and nurse-administered questionnaire pertaining to socio-demographic information, sex-and drug-related risk behaviors, housing conditions, and experiences with the healthcare and criminal justice systems. Participants provide blood samples for serologic HIV testing (or HIV disease monitoring if positive) and HCV testing at each visit. Participants receive \$30 CAD as remuneration at each visit and are offered referrals to addiction treatment and other health services. The VIDUS and ACCESS studies have annual approval from the Providence Health Care Research/University of British Columbia Research Ethics Board. Data for these analyses were collected from December 2005 to May 2015.

Participants who reported ever being on MMT during the last six months at any assessment were included in the study. We compared factors associated with being a “MMT continuer” versus a “MMT discontinuer”. “MMT continuers” were defined as those who reported currently being on MMT at the time of study assessment. “MMT discontinuers” were defined as those who reported being on MMT in the last study assessment but reported not currently being on MMT at the time of study assessment. Of note, some participants may have discontinued MMT more than once during the study period. Baseline characteristics of the “MMT discontinuers” were analyzed only for those who reported discontinuing MMT in the last 6 months at the time of baseline study assessment.

2.2. Variables of interest

The primary endpoint in this analysis was self-reported MMT discontinuation in the last six months (yes vs. no) on the administered questionnaire, defined as reporting accessing methadone at one study visit and reporting not being on methadone at a subsequent study visit. Sociodemographic variables included age, sex (male vs. female), ethnicity (White vs. other race or ethnicity), stable relationship status, defined as being legally married, common-law, or having a regular partner (stable vs. other), education (high school or greater vs. less than high school), and HIV status (HIV-positive vs. HIV-negative). Social-structural risk factors included recent incarceration (yes vs. no), homelessness (yes vs. no), and not accessing government income assistance (yes vs. no). Drug use variables considered included crack cocaine smoking (daily vs.<daily), heroin injection (daily vs. <daily), cocaine injection (daily vs. <daily), prescription opioid injection or non-injection use (daily vs. <daily), methamphetamine use (daily vs. <daily), binge alcohol use (yes vs. no), and binge injection use (yes vs. no). Factors associated with MMT were also considered and included length of time on methadone, defined as the proportion of consecutive follow-ups on MMT relative to the total number of participant follow-ups (>50% vs. 50%), and MMT dose at most recent follow-up prior to MMT discontinuation (or most recent study visit if no

MMT discontinuation was reported) (>60 to 100 mg vs. 60 mg and > 100 mg vs. 60 mg). Records where methadone dosage was missing were removed from analyses. All behaviors referred to activities in the 6 months prior to interview.

2.3. Statistical methods

First, we examined participants' baseline characteristics, stratified by participants who discontinued MMT. For categorical variables, we used Pearson's χ^2 test, and for continuous variables we used Mann-Whitney (Wilcoxon) rank sum test. Second, we examined factors associated with MMT discontinuation in the past six months during study follow-up using Generalized Estimating Equations (GEE) with a logit link function and an exchangeable correlation structure. These methods provide standard errors adjusted by multiple follow-ups per participant using an exchangeable correlation structure for the analysis of correlated data. Therefore, data from every participant follow-up visit were considered in these analyses. As a first step, we used bivariate GEE analyses to determine factors associated with MMT discontinuation. All variables with $p < 0.1$ in bivariate analyses were then entered in the multivariable logistic GEE model. In sub-analyses, among those who reported having discontinued methadone at follow-up, we explored self-reported reasons for methadone discontinuation.

All statistical analyses were performed using R version 3.2.4 (R Foundation for Statistical Computing, Vienna, Austria, 2016). All reported p-values are two-sided and considered significant at $p < 0.05$.

3. RESULTS

From December 2005 to May 2015, 1301 VIDUS and ACCESS participants who accessed MMT were included in the analyses. In total, the study sample consisted of 1301 participants who contributed 9809 observations, of which 121 (1.2%) observations did not include methadone dose and were removed from analysis, leaving a total of 9688 observations. The median number of follow-up assessments was 7 (Interquartile Range [IQR] = 2–12). Among the study sample, 288 (22.1%) participants ever discontinued MMT and 49 (3.8%) discontinued MMT more than once during the study period.

Baseline characteristics of the study sample stratified by MMT discontinuation are presented in Table 1. At study entry, among this sample, 106 (8.1%) participants had discontinued MMT in the past six months. Of those who had discontinued MMT, the median age at baseline was 39 years (IQR = 34–45), 64 (60%) participants were male, and 64 (60%) participants were White.

Bivariate and multivariable GEE analyses of factors associated with MMT discontinuation are presented in Table 2. In bivariable analyses, MMT discontinuation was positively associated with recent homelessness (OR = 2.43, 95% CI: 1.87–3.15), binge alcohol use (OR = 1.48, 95% CI: 1.12–1.96), daily prescription opioid use (OR = 3.02, 95% CI: 1.88–4.84), daily heroin injection (OR = 7.18, 95% CI: 5.62–9.16), daily cocaine injection (OR = 1.85, 95% CI: 1.27–2.69), daily methamphetamine use (OR = 1.75, 95% CI: 1.07–2.85), binge injection drug use (OR = 1.65, 95% CI: 1.25–2.17), recent incarceration (OR = 2.29,

95% CI: 1.64–3.20), and not being on income assistance (OR = 1.98, 95% CI: 1.25–3.14). MMT discontinuation was negatively associated with age (OR = 0.96, 95% CI: 0.95–0.98), having a greater proportion of consecutive follow-ups on MMT (OR = 0.38, 95% CI: 0.29–0.50), being on methadone dose between 60 and 100 mg per day (vs. 60 mg per day) (OR = 0.62, 95% CI: 0.48–0.81) and >100 mg per day (vs. 60 mg per day) (OR = 0.28, 95% CI: 0.20–0.39) at the most recent follow-up.

In multivariable analyses, MMT discontinuation was positively associated with recent homelessness (Adjusted Odds Ratio [AOR] = 1.46, 95% CI: 1.09–1.95), daily heroin injection (AOR = 5.17, 95% CI: 3.82–6.99), daily prescription opioid use (AOR = 2.18, 95% CI: 1.30–3.67), recent incarceration (AOR = 1.46, 95% CI: 1.01–2.12), and not being on any form of income assistance (AOR = 2.14, 95% CI: 1.33–3.46). MMT discontinuation was negatively associated with having a greater proportion of consecutive follow-ups on MMT (AOR = 0.63, 95% CI: 0.47–0.85) and being on methadone dose >100 mg per day (vs. 60 mg per day) at the most recent follow-up visit (AOR = 0.44, 95% CI: 0.31–0.62).

4. DISCUSSION

In this study, 22% of PWUD self-reported MMT discontinuation in the last six months. We identified several potentially modifiable social-structural factors that were associated with MMT discontinuation, including recent homelessness, recent incarceration, and not receiving income assistance. Frequent (i.e. daily) heroin injection use and prescription opioid use were also associated with MMT discontinuation.

The rate of MMT discontinuation in our study (22%) was lower than has been observed in other settings, where six-month retention rates typically range from 46 to 65% (Farré, Mas, Torrens, Moreno, & Camí, 2002; Magura et al., 1998; Nosyk et al., 2010; Reisinger et al., 2009). MMT provision in the province of British Columbia, Canada, is provided in the setting of ‘low threshold’ programs, where efforts are made to minimize barriers to service access, including through use of pharmacy-delegated methadone delivery services and outreach models of care, and by not requiring abstinence from drug use as a condition of MMT access (Mofizul Islam, Topp, Conigrave, & Day, 2013). We hypothesize that the ‘low threshold’ service provision model for MMT in our setting may contribute to the lower MMT discontinuation rates observed in our study.

There was a positive association observed between MMT discontinuation and recent homelessness in this study. Previous research has demonstrated socioeconomic factors impact adherence to addiction treatment (Haskew, Wolff, Dunn, & Bearn, 2008; Roux et al., 2014; Shen et al., 2016). For example, Kerr, Marsh, Li, Montaner, and Wood (2005) found that individuals who have access to stable housing remained on MMT for at least one year longer than those without access to housing (Kerr et al., 2005). Unstably-housed individuals with substance use disorder(s) often describe the need to prioritize access to food and shelter over MMT adherence (Paudyal et al., 2017). Furthermore, stable housing may allow individuals to have a more predictable structured time to visit pharmacies for daily witnessed dispensing. “Housing first” initiatives, in which rental apartments are provided to people experiencing homelessness and mental illness have been shown to improve housing stability

and may facilitate retention on MMT (Appel, Tsemberis, Joseph, Stefancic, & Lambert-Wacey, 2012). For those who face ongoing barriers to housing, outreach strategies such as intensive case management have also been shown to be an effective retention approach (Coviello, Zanis, Wesnoski, & Alterman, 2006).

The association between incarceration and MMT discontinuation has also been well-described elsewhere, and qualitative studies suggest this may be due to barriers to MMT continuity during transitions between custodial and community settings (Small, Wood, Betteridge, Montaner, & Kerr, 2009). There remain significant barriers to initiating and accessing opioid agonist therapies in custodial settings, and previous research has shown that the majority of individuals with OUD do not have access to MMT while incarcerated (Larney & Dolan, 2009; Bazazi et al., 2017 ; Bozinoff, Small, Long, DeBeck & Fast, 2017). This is particularly concerning given that incarcerated individuals with OUD are at high risk for relapse and fatal overdose in the year post-release, especially in the first month after leaving an incarcerated setting (Binswanger et al., 2007 ; Kinlock et al., 2007 ; Krinsky, Lathrop, Brown, & Nolte, 2009). Additionally, previous studies have found ancillary benefits to MMT continuation post-release, including reduced HIV transmission (Larney & Dolan, 2009), a significantly longer time to re-arrest (Westerberg, McCrady, Owens, & Guerin, 2016), and greater treatment engagement after release, which could in turn reduce the risk of death from drug-related risk behaviors and overdose (Rich et al., 2015). Given the known risks associated with MMT discontinuation post-release, efforts to provide MMT to OUD individuals during transitions from custodial to community settings are crucial.

In the province of B.C., residents who receive income assistance through the Ministry of Social Development and Poverty Reduction (MHSD) have extended drug coverage, with 100% of costs covered for MMT (“Fair PharmaCare Plan - Province of British Columbia”, 2018). The eligibility criteria for income assistance qualification is determined by the MHSD through a complex calculation of basic income and needs. Individuals who don’t meet criteria for income assistance are required to pay for a percentage of methadone drugs costs based on income. We surmise that the positive association between not receiving income assistance and MMT discontinuation may reflect financial barriers to accessing MMT among those who do not access income assistance. However, opioid agonist therapies (including methadone, buprenorphine/naloxone, and slow-release oral morphine) were recently added to the provincial Psychiatric Medications Plan, allowing patients with an annual income less than \$42,000 CAD to access these medications for free. This plan helps reduce financial barriers to accessing medications for opioid use disorder, thus better aligning with WHO recommendations that all eligible individuals be able to access MMT (World Health Organization, 2015).

There were strong positive associations between MMT discontinuation and frequent injection heroin and prescription opioid use. As this is a cohort study and causality cannot be inferred, it may be that participants use more illicit opioids following MMT discontinuation or that individuals with heavy illicit opioid use have more severe OUD and represent a population who may be less likely to successfully be retained on MMT (Duffy & Mackridge, 2013; Peles, Schreiber, & Adelson, 2010). This study also found negative associations between MMT discontinuation and being on higher doses of methadone (i.e.

>60 mg per day) and being on longer duration of MMT consistent with previous research (Nosyk et al., 2009). Despite this knowledge, MMT dosing often remains below recommended therapeutic targets. One US national study found that only 23% of participants received MMT doses above 60 mg per day (D'Aunno, Pollack, Frimpong, & Wuchiett, 2014). Similarly, a study in our setting found that 50% of MMT participants received mean daily doses below 60 mg per day (Nosyk et al., 2009). Furthermore, higher MMT dose has been associated with better ART adherence (Lappalainen et al., 2015). These findings underscore the need to support patients and prescribers in targeting optimal MMT dosing to support treatment retention.

4.1. LIMITATIONS

There are several limitations to our study. First, VIDUS and ACCESS are not random samples and cannot be presumed to be wholly representative of the PWUD population in Vancouver or elsewhere. Second, MMT discontinuation events and reasons for discontinuation were self-reported by study participants and may be impacted by recall bias. Third, the duration of the MMT before it was discontinued could not be determined based on the nature of the study. Fourth, our statistical methods considered associations between MMT discontinuation and various independent variables over time. The exact temporal relationship between the outcome of interest and the independent variables cannot be ascertained and therefore this study does not allow for a thorough investigation of causal relationships. In sub-analyses, not all study participants reported a discontinuation reason, and reported reasons were not studied qualitatively.

5. CONCLUSIONS

In conclusion, discontinuation of MMT in this urban setting was associated with several social-structural exposures, including recent homelessness, incarceration, lack of social income assistance, as well as heavy opioid and comorbid substance use. Our findings propose several potential directions to support retention on MMT, including access to housing and outreach services to support low threshold methadone treatment, removal of financial barriers to accessing MMT, as well as efforts to support MMT continuation between community and custodial settings.

Acknowledgements

The authors thank the study participants for their contributions to the research, as well as current and past researchers and staff. We would specifically like to thank: Tricia Collingham, Jennifer Matthews and Steve Kain for their research and administrative assistance.

Funding

The study was supported by the US National Institutes of Health (U01DA038886 and U01DA021525). This research was undertaken, in part, thanks to funding from the Canada Research Chairs program through a Tier 1 Canada Research Chair in Inner City Medicine which supports Dr. Evan Wood. Dr. Nadia Fairbairn is supported by a Michael Smith Foundation for Health Research (MSFHR)/St. Paul's Foundation Scholar award. Dr. Kanna Hayashi is supported by the Canadian Institutes of Health Research (CIHR) New Investigator Award (MSH-141971), a MSFHR Scholar Award, and the St. Paul's Hospital Foundation. M-J Milloy is supported by a Scholar Award from MSFHR and a New Investigator Award from CIHR.

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Highlights

- Modifiable risk factors for MMT discontinuation were explored.
- MMT discontinuation was positively associated with homelessness, incarceration.
- Efforts to ensure MMT provision in custodial settings are important.

Table 1.Baseline characteristics of a sample of people who inject drugs stratified by MMT discontinuation ($n=1301$).

Characteristic	MMT discontinuation		OR (95% CI)	<i>p</i> -Value
	Yes <i>n</i> = 106 (8.1%)	No <i>n</i> = 1195 (91.9%)		
Age				
Median (IQ range)	39 (34–45)	42 (35–48)	0.97 (0.95–0.995)	0.012
Sex				
Female	42 (8.2)	466 (91.7)	0.98 (0.65–1.46)	0.904
Male	64 (8.1)	728 (91.9)		
White				
No	42 (8.8)	437 (91.2)	0.88 (0.58–1.32)	0.532
Yes	64 (7.8)	758 (92.2)		
Homeless^a				
No	51 (5.8)	833 (94.2)	2.50 (1.68–3.74)	<0.001
Yes	55 (13.3)	359 (86.7)		
Binge alcohol use^a				
No	79 (7.4)	992 (92.6)	1.62 (1.01–2.58)	0.043
Yes	26 (11.4)	202 (88.6)		
Daily non-injection crack use^a				
No	70 (8.8)	726 (91.2)	0.80 (0.53–1.21)	0.289
Yes	36 (7.1)	468 (92.9)		
Daily heroin injection^a				
No	36 (3.9)	892 (96.1)	5.76 (3.78–8.79)	<0.001
Yes	70 (18.9)	301 (81.1)		
Daily cocaine injection^a				
No	91 (7.9)	1064 (92.1)	1.37 (0.77–2.44)	0.282
Yes	15 (10.5)	128 (89.5)		
Daily methamphetamine use^a				
No	94 (7.6)	1138 (92.3)	2.69 (1.39–5.20)	0.002
Yes	12 (18.2)	54 (81.8)		
Daily opioid use^a				
No	84 (6.9)	1129 (93.1)	4.69 (2.75–8.00)	<0.001
Yes	22 (25.9)	63 (74.1)		
Binge injection drug use^a				
No	69 (7.1)	905 (92.9)	1.65 (1.08–2.51)	0.020
Yes	36 (11.2)	287 (88.9)		
Incarceration^a				
No	78 (7.1)	1020 (92.9)	2.10 (1.33–3.34)	0.001
Yes	28 (13.9)	174 (86.1)		

Characteristic	MMT discontinuation		OR (95% CI)	p-Value
	Yes <i>n</i> = 106 (8.1%)	No <i>n</i> = 1195 (91.9%)		
HIV^a				
No	80 (9.93)	726 (90.07)	0.50 (0.32–0.79)	0.003
Yes	26 (5.25)	469 (94.75)		
No income assistance^a				
No	96 (7.8)	1105 (92.0)	1.46 (0.73–2.91)	0.282
Yes	10 (11.2)	79 (88.8)		
Proportion of visits on MMT^b				
>50%	57 (12.5)	398 (87.5)	0.43 (0.29–0.64)	<0.001
50%	49 (5.8)	797 (94.2)		
Methadone dose^d				
>60 to 100 mg	21 (5.7)	347 (94.3)	1.08 (0.59–1.98)	0.813
>100 mg	8 (2.0)	392 (98.0)	0.36 (0.16–0.82)	<0.001
60 ^c	23 (5.3)	409 (94.7)		

^aDenotes activities in the previous 6months.

^bProportion of follow-up visits on methadone (>50% vs. 50%).

^cReference group.

^dMissing values for methadone dose variable (*n*=52 for 'Yes', *n*=1148 for 'No').

Table 2.Bivariable and multivariable GEE* analyses of factors associated with MMT discontinuation ($n=1301$).

Characteristic	Odds Ratio (95% CI)	<i>p</i> -Value	Adjusted Odds Ratio (95% CI)	<i>p</i> -Value
Age (yes vs. no)	0.96 (0.95–0.98)	<0.001	0.99 (0.98–1.01)	0.266
Sex (female vs. male)	1.06 (0.81–1.39)	0.674		
White (yes vs. other)	1.05 (0.80–1.39)	0.718		
Homelessness ^a (yes vs. no)	2.43 (1.87–3.15)	<0.001	1.46 (1.09–1.95)	0.011
Binge alcohol use ^a (yes vs. no)	1.48 (1.12–1.96)	0.006	1.30 (0.97–1.74)	0.080
Daily crack cocaine ^a (noninjection) (yes vs. no)	1.18 (0.90–1.54)	0.241		
Daily opioids ^a (yes vs. no)	3.02 (1.88–4.84)	<0.001	2.18 (1.30–3.67)	0.003
Daily heroin injection ^a (yes vs. no)	7.18 (5.62–9.16)	<0.001	5.17 (3.82–6.99)	<0.001
Daily cocaine injection ^a (yes vs. no)	1.85 (1.27–2.69)	<0.001	0.90 (0.59–1.35)	0.594
Daily methamphetamine use ^a (yes vs. no)	1.75 (1.07–2.85)	0.025	1.02 (0.61–1.69)	0.951
Binge on drug injection ^a (yes vs. no)	1.65 (1.25–2.17)	<0.001	0.98 (0.72–1.33)	0.897
HIV ^a (yes vs. no)	0.76 (0.58–1.01)	0.063	0.92 (0.70–1.20)	0.518
Incarceration (yes vs. no)	2.29 (1.64–3.20)	<0.001	1.46 (1.01–2.12)	0.046
No Income assistance (yes vs. no)	1.98 (1.25–3.14)	0.004	2.14 (1.33–3.46)	0.002
Proportion of visits on MMT (>50% vs. 50%)	0.38 (0.29–0.50)	<0.001	0.63 (0.47–0.85)	0.002
Methadone dose >60 to 100 mg vs 60 mg	0.62 (0.48–0.81)	<0.001	0.78 (0.59–1.03)	0.084
>100 mg vs 60 mg	0.28 (0.20–0.39)	<0.001	0.44 (0.31–0.62)	<0.001

* Generalized Estimating Equations.

^aDenotes activity in the previous 6months.