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Factors associated with discontinuation of methadone maintenance therapy (MMT) among persons who use alcohol in Vancouver, Canada

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Abstract

Background: We sought to examine the factors associated with discontinuation of MMT among persons on methadone who use alcohol.

Methods: We evaluated the impact of drug-related and other factors on discontinuation of MMT among persons enrolled in MMT and who reported any use of alcohol, and who were enrolled in two community-recruited prospective cohorts of people who use illicit drugs (PWUD). Extended Cox models with time-dependent variables identified factors independently associated with time to first MMT discontinuation.

Results: Between December 2005 and 2015, 823 individuals on MMT also reported using alcohol at least once, were included in these analyses. During the study period, 391 (47.5%) discontinued methadone. Daily heroin injection (Adjusted Hazard Ratio [AHR]= 2.67, 95% Confidence Interval [CI]: 2.10 – 3.40) and homelessness (AHR= 1.42, 95% CI: 1.10 – 1.83) were positively associated with MMT discontinuation, whereas receiving other concurrent addiction treatment in addition to MMT (AHR= 0.07, 95% CI: 0.05 – 0.08), as well as >60 mg methadone dose (AHR = 0.48, 95% CI: 0.39 – 0.60); Hepatitis C virus seropositivity (AHR= 0.65, 95% CI: 0.47 – 0.90); and HIV seropositivity (AHR= 0.72, 95% CI: 0.57 – 0.91) were negatively associated with MMT discontinuation. Any/ heavy alcohol use was not independently associated with MMT discontinuation.

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Contributors

JK and EW conducted the analysis and drafted the manuscript. EN analyzed the data. SN, RP, KH, MJSM and TK audited the analysis, reviewed the draft and suggested improvements. All authors read and approved the final version of the manuscript.

Author Disclosures

Conflict of Interest

No conflict declared

Conclusions: This study reinforces the known risks of continued heroin injection and homelessness for MMT discontinuation among individuals who also consume alcohol and highlights the protective effect of both MMT dose and receipt of concurrent addiction treatment.

Keywords

alcohol; methadone; substance-related disorders; treatment outcomes

BACKGROUND

Opioid use disorder (OUD) contributes to harms to individuals the society and the health care system (Degenhardt et al., 2013). It often co-occurs with other forms of substance use and thus can exacerbate the risk for fatal overdose and other harms (Degenhardt and Hall, 2012). Opioid agonist therapy (OAT) with methadone (i.e., methadone maintenance treatment [MMT]) has been shown to reduce illicit drug, all-cause and overdose mortality among people with opioid use disorders (Mattick et al., 2009). Retention in OAT is generally an important determinant of treatment success (Sordo et al., 2017). Factors associated with attrition from treatment include a range of barriers such as homelessness, poverty, mental health disorders and lack of general support (Farre et al., 2002).

There is a high prevalence of concurrent alcohol and other drug use among persons on MMT (Hartzler et al., 2010; Soyka, 2015). However, while ongoing illicit drug use is associated with MMT discontinuation, the role of alcohol use and MMT discontinuation has received far less attention (Staiger et al., 2013). Importantly, some OAT programs may refuse to provide treatment to persons with ongoing alcohol use disorder (AUD), since co-use of alcohol with opioids, such as methadone, is a well-known risk factor for fatal overdose (Nolan et al., 2016). These concerns suggest that greater attention should be paid to the impact of alcohol use and other factors affecting MMT discontinuation among persons who also use alcohol. Therefore, we sought to examine factors associated with discontinuation of MMT among this population.

METHODS

We obtained data from two prospective cohorts of people who use illicit drugs (PWUD) in Vancouver, Canada: the Vancouver Injection Drug Users Study (VIDUS) and the AIDS Care Cohort to evaluate Exposure to Survival Services (ACCESS). Their methods have been described elsewhere (Kerr et al., 2008; Strathdee et al., 1998). In brief, VIDUS includes HIV-seronegative adults who have injected an illicit drug in month prior to enrolment. ACCESS enrolls HIV-seropositive adults who have used an illicit drug other than (or in addition to) cannabis in previous month at recruitment. Both cohorts recruit potential participants via snowballing and street outreach. The harmonized questionnaires assess identical demographic characteristics, drug use characteristics and associated exposures at baseline and bi-annually thereafter. Serologic tests for HIV and hepatitis C (HCV) antibodies, and HIV disease monitoring, where appropriate, are also performed. A \$30 CDN stipend rewards participants for their time given at each interview. University of British

Columbia/Providence Health Care Research Ethics Board approved both studies and all respondents provide informed consent at baseline.

This study included participants who: (1) were recruited between December 1, 2005 and May 31, 2015 and had at least one follow up visit after baseline visit; (2) reported having ever injected drugs at baseline; (3) reported receiving methadone in past six months at baseline; and (4) reported using alcohol at least once during study period.

The primary endpoint was time to the first MMT discontinuation, defined as “not being currently on MMT” at the time of interview. As in previous articles (Klimas et al., 2016), the date of MMT discontinuation was estimated using the midpoint between the last negative and the first reported date of MMT discontinuation. We did not consider recurrent episodes of MMT. We selected several characteristics as explanatory variables based on previous studies that identified potential predictors of MMT discontinuation (Backmund et al., 2003; Nyamathi et al., 2009). These included: age (per year older); gender (male vs. non-male); ethnicity (white vs. non-white); baseline depression, as measured by the Center for Epidemiologic Studies Depression scale (CES-D) (CES-D score of 22 vs. <22); homelessness (yes vs. no); stable relationship (legally married/common law/regular partner vs. other); heroin injection (daily vs. < daily); crystal methamphetamine injection (daily vs. <daily); cocaine injection (daily vs. <daily); cannabis use (daily vs. <daily); HIV serostatus (positive vs. negative); HCV serostatus (positive vs. negative); recent incarceration (yes vs. no); non-fatal overdose (yes vs. no); receiving any other treatment for substance use disorder (SUD) in addition to MMT (“In last six months, have you been in any kind of alcohol or drug treatment, excluding methadone / Methadose or Suboxone?” yes vs. no); ever been diagnosed with a mental illness (yes vs. no); being a victim of violence (yes vs. no); and assaulted anyone (yes vs. no). While gender, white ethnicity, depression CES-D score were assessed at baseline, all other variables were assessed and referred to the six-month period prior to follow-up interview. Heavy alcohol use (yes vs. no) was characterized using the National Institute on Alcohol Abuse and Alcoholism (NIAAA) definition (> 3 standard drinks per occasion, or > 7 drinks per week for females; > 4 drinks per occasion, or > 14 drinks per week for males)(National Institute on Alcohol Abuse and alcoholism (NIAAA), 2010). MMT dosage was lagged (lagged MMT dose ≥ 60 vs. lagged MMT dose < 60) by one follow-up assessment and referred to six months prior to the follow-up questionnaire up until one immediately preceding the first report of MMT discontinuation.

An extended Cox model examined bivariable and multivariable associations between explanatory variables and time to MMT discontinuation. First, we compared all explanatory variables with time to MMT discontinuation in bivariable analysis. Then, we constructed multivariable Cox regression models using a backward model fitting a protocol defined *a priori* from the examination of the Akaike information criterion (AIC) and type III *p*-values. First, all explanatory variables were included in the initial multivariable model. Following examination of the AIC value of models, we eliminated the variable with the largest *p*-value and constructed an abridged model. We selected the multivariable models with the lowest AIC value, based on repeated iterations of the process described above. All *p*-values were

two-sided. All statistical analyses were performed using the R version 0.99.892 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

In total, 1193 participants (8457 observations) were included in these analyses, of whom 823 (69%, 6456 observations) were eligible for the study, i.e., enrolled in MMT and reported alcohol use at least once during the study. These 823 participants were followed up for a median of 42.15 months (Inter-quartile range [IQR]: 15.45–88.37) between December 2005 and May 2015. Among the 823 participants, 391 (47.5%) discontinued MMT during the study period. Table 1 shows baseline characteristics. As shown in Table 1, most participants were white (526, 63.9%), male (495, 60.1%), with the median age of 42 (IQR: 35.8 – 47.9) years; their mean lagged methadone dose was 49 mg (Standard Deviation [SD] = 110.2 mg), and 119 mg (SD = 102.8 mg), for those on <60 mg and on >60 mg doses, respectively.

As shown in Table 2, daily heroin injection (Adjusted Hazard Ratio [AHR] = 2.67, 95% Confidence Interval [CI]: 2.10 – 3.40) and homelessness (AHR = 1.42, 95% CI: 1.10 – 1.83) were independently and positively associated with MMT discontinuation, whereas receiving other concurrent SUD treatment in addition to MMT (AHR = 0.07, 95% CI: 0.05 – 0.08); methadone dose >60 mg (AHR = 0.48, 95% CI: 0.39 – 0.60); HCV seropositivity (AHR = 0.65, 95% CI: 0.47 – 0.90); and HIV seropositivity (AHR = 0.72, 95% CI: 0.57 – 0.91) were negatively associated with MMT discontinuation. Although heavy alcohol use was independently associated with MMT discontinuation in the bivariable analysis (HR = 1.41, 95% CI: 1.09 – 1.83), it was not independently associated with MMT discontinuation (AHR = 0.93, 95% CI: 0.69 – 1.26) in the multivariable analysis.

DISCUSSION

In this study involving individuals on MMT who reported alcohol co-use, we found that continued daily heroin injection and homelessness predicted discontinuation of MMT, whereas concurrent treatment for SUD in addition to MMT, HCV seropositivity, HIV seropositivity and methadone dose >60 mg were all negatively associated with MMT discontinuation. Interestingly, any alcohol use and heavy alcohol use did not predict MMT discontinuation.

Our research has limitations. We did not recruit participants randomly and, therefore, our sample may not be representative of all persons who co-use alcohol in the MMT. Much of the data in this study was ascertained through participant self-report, which would likely alter the study findings towards the null hypothesis, though past research suggests that self-report of PWUD is largely valid (Darke, 1998). Current methadone status was a yes/no question based on the past six months. Therefore, if a person who was not on methadone at baseline, but had been sometime during the last six months, they have been counted as being currently on methadone. **While we sought to address this bias with multivariate adjustment of the key demographic and behavioral predictors of discontinuation, there may be residual confounding. More specifically, our analysis should be taken with caution and knowing the exact date of the discontinuation would require study**

triangulating with clinic attendance data. Because the HIV and HCV infections are tightly linked, little could have been done to limit their collinearity. Furthermore, the observational nature of the included cohort studies precludes inferences about causality; unmeasured factors may confound the results. Finally, we did not know the exact date of the MMT enrolment and discontinuation and did not validate alcohol consumption with breath or urine tests, although questionnaires may be better to detect current use than laboratory tests (Aertgeerts et al., 2002).

Our study's finding that methadone dose >60 mg was negatively associated with MMT discontinuation is supported by previous research highlighting the dose-response effect of MMT and retention in treatment (Strain et al., 1999). The dose is directly linked to treatment retention, lack of which is a risk factor for fatal overdose and overdose often involves alcohol co-ingestion (Jones et al., 2014; Sordo et al., 2017). While existing literature has broadly examined the effects of methadone on alcohol use, the impact of continued drug use and other factors on MMT discontinuation among persons with alcohol co-use (and heavy alcohol use) has largely been overlooked (Soyka, 2015; Staiger et al., 2013). For instance, while short-term MMT (i.e., 4 weeks) appeared to reduce alcohol consumption in a study of persons without a diagnosis of AUD (Bickel and Rizzuto, 1991), another study of longer-term MMT (i.e., two years) appeared to increase alcohol consumption, potentially as a compensatory substance (Dobler-Mikola et al., 2005).

Finally, the lack of association between heavy alcohol use and MMT discontinuation also provides further support to proponents of allowing people who also consume alcohol to continue accessing MMT. Persons on MMT who also consume alcohol may have protected retention if they seek concurrent treatment. These findings highlight the need for additional interventions aimed at ensuring continuity of MMT among persons who co-use alcohol.

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Highlights

- This study reinforces the known risks of continued heroin injection and homelessness for MMT discontinuation among individuals who also consume alcohol and highlights the protective effect of both MMT dose and receipt of concurrent addiction treatment.
- Daily heroin injection and homelessness were positively associated with MMT discontinuation, whereas receiving other concurrent addiction treatment in addition to MMT, as well as >60 ml methadone dose; Hepatitis C virus seropositivity; and HIV seropositivity were negatively associated with MMT discontinuation.
- Heavy alcohol use was not independently associated with MMT discontinuation.

TABLE 1.Baseline demographics of study participants stratified by MMT discontinuation ($n=823$)

Characteristic	MMT discontinuation at least once during study			<i>p</i> - value
	Total (%) (<i>n</i> = 823)	Yes (%) 391 (45.6)	No (%) 432 (54.4)	
Age				
Median (IQR)	42 (35.8–47.9)	41 (34.5–47.0)	43 (36.4–48.5)	0.007
Ethnicity				
White	526 (63.9)	243 (62.1)	283 (65.5)	0.316
Non-white	297 (36.1)	148 (37.9)	149 (34.5)	
Gender				
Male	495 (60.1)	241 (61.6)	254 (58.8)	0.406
Non-male	328 (39.9)	150 (38.4)	178 (41.2)	
CESD depression score (≥ 22)				
yes	443 (53.8)	216 (55.2)	227 (52.5)	0.310
no	272 (33.0)	122 (31.2)	150 (34.7)	
Homelessness[†]				
yes	241 (29.3)	127 (32.5)	114 (26.4)	0.055
no	580 (70.5)	263 (67.3)	317 (73.4)	
Stable relationship[†]				
yes	265 (32.2)	136 (34.8)	129 (29.9)	0.154
no	550 (66.8)	253 (64.7)	297 (68.8)	
Daily injection heroin use[†]				
yes	182 (22.1)	96 (24.6)	86 (19.9)	0.109
no	641 (77.9)	295 (75.4)	346 (80.1)	
Daily injection cocaine use[†]				
yes	76 (9.2)	39 (10.0)	37 (8.6)	0.492
no	746 (90.6)	352 (90.0)	394 (91.2)	
Daily injection crystal meth use[†]				
yes	37 (4.5)	16 (4.1)	21 (4.9)	0.600
no	785 (95.4)	374 (95.7)	411 (95.1)	
Daily cannabis use[†]				
yes	165 (20.0)	73 (18.7)	92 (21.3)	0.339
no	657 (79.8)	318 (81.3)	339 (78.5)	
Non-fatal overdose[†]				
yes	56 (6.8)	27 (6.9)	29 (6.7)	0.897
no	765 (93.0)	362 (92.6)	403 (93.3)	
HIV serostatus				
positive	315 (38.3)	120 (30.7)	195 (45.1)	<0.0001
negative	508 (61.7)	271 (69.3)	237 (54.9)	

Characteristic	MMT discontinuation at least once during study			<i>p</i> - value
	Total (%) (<i>n</i> = 823)	Yes (%) 391 (45.6)	No (%) 432 (54.4)	
HCV serostatus				
positive	740 (89.9)	341 (87.2)	399 (92.4)	0.019
negative	82 (10.0)	49 (12.5)	33 (7.6)	
Recent incarceration[†]				
yes	129 (15.7)	69 (17.6)	60 (13.9)	0.134
no	693 (84.2)	321 (82.1)	372 (86.1)	
Ever been diagnosed with a mental illness				
yes	442 (53.7)	204 (52.2)	238 (55.1)	0.402
no	381 (46.3)	187 (47.8)	194 (44.9)	
Treatment other than MMT[†]				
yes	767 (93.2)	366 (93.6)	401 (92.8)	0.656
no	56 (6.8)	25 (6.4)	31 (7.2)	
Attacked, assaulted, or suffered violence[†]				
yes	171 (20.8)	87 (22.3)	84 (19.4)	0.329
no	649 (78.9)	303 (77.5)	346 (80.1)	
Assaulted anyone[†]				
yes	98 (11.9)	45 (11.5)	53 (12.3)	0.660
no	700 (85.1)	338 (86.4)	362 (83.8)	
Alcohol use categories[†]				
No alcohol [*]	316 (38.4)	150 (38.4)	166 (38.4)	0.060
Alcohol use	409 (49.7)	184 (47.1)	225 (52.1)	
Heavy alcohol use	98 (11.91)	57 (14.6)	41 (9.5)	
Lagged MMT dose^{††}				
lagged MMT dose $\geq$ 60	233 (28.31)	142 (36.32)	91 (21.06)	0.000
lagged MMT dose<60	564 (68.53)	227 (58.06)	337 (78.01)	

[†] Denotes activities in the previous 6 months. CI= 95% confidence interval; MMT= methadone maintenance therapy;

^{††} To ensure that the current MMT dose preceded the estimated initiation of MMT discontinuation, it was lagged by 1 follow-up assessment and referred to the 6 months prior to the follow-up questionnaire(s) up until 1 immediately preceding the 1st report of MMT discontinuation.

^{*} Although we restricted the sample to persons who used alcohol at least once during the study, some individuals did not use alcohol at baseline, but then used it during the follow up.

TABLE 2:

Bivariable and multivariable extended Cox regression analyses of variables independently associated with time to first MMT discontinuation among a sample of participants who also report alcohol use ($n= 823$).

Characteristic	Unadjusted		Adjusted	
	Hazard Ratio (95% CI)	<i>p</i> - value	Hazard Ratio (95% CI)	<i>p</i> - value
Age (Per one year older)	0.98 (0.96–0.9)	0.0002		
Ethnicity (White vs. non-white)	0.85 (0.69–1.05)	0.1331		
Gender (male vs. non-male)	1.05 (0.86–1.29)	0.6268		
CESD depression score at baseline (>22 vs. <22)	1.11 (0.90–1.39)	0.3330		
Homelessness [†] (yes vs. no)	1.67 (1.32–2.11)	<0.0001	1.42 (1.10–1.83)	0.007
Stable relationship [†] (yes vs. no)	0.93 (0.75–1.15)	0.4952		
Daily injection heroin use [†] (yes vs. no)	4.74 (3.83–5.86)	<0.0001	2.67 (2.10–3.40)	<0.0001
Daily injection cocaine use [†] (yes vs. no)	1.26 (0.87–1.82)	0.2226		
Daily injection crystal meth use [†] (yes vs. no)	1.39 (0.90–2.13)	0.1355		
Daily cannabis use [†] (yes vs. no)	0.84 (0.64–1.11)	0.2287		
Non-fatal overdose [†] (yes vs. no)	1.66 (1.11 –2.46)	0.0128		
HIV serostatus (yes vs. no)	0.66 (0.54–0.82)	0.0001	0.72 (0.57–0.91)	0.005
HCV serostatus (yes vs. no)	0.48 (0.35–0.66)	<0.0001	0.65 (0.47–0.90)	0.009
Recent incarceration [†] (yes vs. no)	1.37 (0.99–1.90)	0.0599		
Ever been diagnosed with a mental illness at baseline (yes vs. no)	0.94 (0.77–1.15)	0.5600		
Treatment other than MMT [†] (yes vs. no)	0.05 (0.04–0.07)	<0.0001	0.07 (0.05–0.08)	<0.0001
Attacked, assaulted, or suffered violence [†] (yes vs. no)	1.12 (0.86–1.47)	0.3892		

Characteristic	Unadjusted		Adjusted	
	Hazard Ratio (95% CI)	p - value	Hazard Ratio (95% CI)	p - value
Assaulted anyone [†] (yes vs. no)	1.17 (0.81 – 1.70)	0.4082		
Any alcohol use (yes vs. no)	1.49 (1.22–1.84)	0.0001		
Heavy alcohol use [†] (yes vs. no)	1.41 (1.09–1.83)	0.0096		
Lagged MMT dose ^{†*} (lagged MMT dose>=60 vs. lagged MMT dose<60)	0.35 (0.29 – 0.43)	<0.0001	0.48 (0.39 – 0.60)	<0.0001

[†]Denotes activities in the previous 6 months. CI= confidence interval; MMT= methadone maintenance therapy;

^{†*}To ensure that the current MMT dose preceded the estimated initiation of MMT discontinuation, it was lagged by 1 follow-up assessment and referred to the 6 months prior to the follow-up questionnaire(s) up until 1 immediately preceding the 1st report of MMT discontinuation.