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The Impact of Enrolment in Methadone Maintenance Therapy on Initiation of Heavy Drinking among People who Use Heroin

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ABSTRACT

Background: There is equivocal evidence regarding whether people who use heroin substitute heroin for alcohol upon entry to methadone maintenance therapy (MMT). We aimed to examine the impact of MMT enrolment on the onset of heavy drinking among people who use heroin.

Methods: We derived data from prospective, community-based cohorts of people who inject drugs in Vancouver, Canada, between December 1, 2005 and May 31, 2014. Multivariable extended Cox regression analysis examined the effect of MMT enrolment on the onset of heavy drinking among people who used heroin at baseline.

Results: In total, 357 people who use heroin were included in this study. Of these, 208 (58%) enrolled in MMT at some point during follow-up, and 115 (32%) reported initiating heavy drinking during follow-up for an incidence density of 7.8 events [95% confidence interval (CI) = 6.4–9.5] per 100 person-years. The incidence density of heavy drinking was significantly lower among those reported MMT enrolment at some point during follow-up compared to those who did not (4.6 vs. 16.2; $p < 0.001$). MMT enrolment was not significantly associated with time to initiate heavy drinking (adjusted relative hazard = 1.27; 95% CI = 0.78 – 2.07) after adjustment for relevant demographic and substance-use characteristics. Age and cannabis use were the only variables that were independently associated with the time to onset of heavy drinking (ARH = 0.74; 95% CI = 0.58 – 0.94) and (ARH = 2.06; 95% CI = 1.32 – 3.19), respectively.

Conclusion: In this study, MMT enrolment did not predict heavy drinking and may even appear to decrease the initiation of heavy drinking. Our findings suggest younger age and cannabis use may predict heavy drinking. These findings could help inform on-going discussions about the effects of opioid agonist therapy on alcohol consumption among people who use heroin.

Word Count: 296

Keywords: alcohol; methadone maintenance treatment; heroin; longitudinal study

Introduction

Heroin use continues to drive mental and physical morbidity and mortality globally and frequently goes along with concomitant substance use disorders [1,2]. Methadone maintenance therapy (MMT) has been shown to reduce morbidity and mortality among people who use heroin and other opiates [3,4]; however, previous studies have suggested a high prevalence of heavy alcohol use among MMT patients [5-7], and interventions to reduce heavy drinking in this population are lacking [8]. MMT patients who engage in heavy alcohol use do not appear to benefit from MMT to the same extent as those who do not, and most of them develop further complications [9-11]. Many patients overdose because of alcohol [12,13]. While recent systematic reviews have indicated that alcohol, heroin and methadone are correlated, the impact of enrolment in MMT on heavy drinking has not been fully characterized [5,14,15]. Phases of heavy drinking seem to follow after bouts of abstinence from heroin use, and this pattern often repeats over time [16]. However, specifics of this relationship remain unclear. Therefore, we undertook this longitudinal study to examine whether the enrolment in MMT was associated with the initiation of heavy alcohol use among people who use heroin who were not engaged in heavy alcohol use or enrolled in MMT at baseline.

Methods

We obtained data for this analysis from two prospective cohorts of people who use drugs 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 elsewhere [17-19]. Briefly, VIDUS is a cohort of HIV-seronegative adults who have injected an illicit drug in the month prior to the baseline interview. ACCESS enrols HIV-seropositive adult drug users who have used an illicit drug other than cannabis in the previous month at baseline.

Both cohorts recruit through snowballing and street outreach. Both cohorts use harmonized questionnaires at baseline and bi-annually thereafter that include demographic characteristics, drug use patterns and related exposures. The follow-up assessments were conducted approximately every six months. The missed assessments were managed as missing values in the data analysis. Serologic testing for HIV and HCV antibodies, and HIV disease monitoring, as appropriate, is also conducted. To compensate participants for their time, a $30 CDN stipend was given at each interview. The University of British Columbia/Providence Healthcare Research Ethics Board approved both studies and all respondents signed an informed consent at baseline.

The present study included participants who: (1) were recruited between December 1, 2005 and May 31, 2014 and have at least one follow-up visit; (2) reported having ever injected drugs at baseline; (3) reported any heroin use in the past six months at baseline; (4) reported not being enrolled in MMT in the past six months at baseline; and (5) did not report the National Institute on Alcohol Abuse and Alcoholism (NIAAA)-defined heavy alcohol use in the past six months at baseline. NIAAA defines heavy alcohol use as an average of >three drinks per occasion, or >seven drinks per week, among females, and an average of >four drinks per occasion, or >14 drinks per week, among males [20].

The primary endpoint was time to initiation of NIAAA-defined heavy alcohol use. The date of initiation was estimated using the midpoint between the last negative and the first affirmative reports of heavy alcohol use in the previous six months before baseline or a follow-up assessment. The primary explanatory variable of interest was the enrolment in MMT in the previous six months before a follow-up assessment. We also selected other demographic, behavioural and health characteristics as secondary explanatory variables based on previous studies that identified potential predictors of changes in alcohol consumption in relation to

addiction treatment [21-24]. These included: age (per year older); gender (male *vs.* female); ethnicity/ancestry (Caucasian *vs.* Aboriginal *vs.* others); baseline depression, as measured by the Center for Epidemiologic Studies Depression scale (CES-D) (CES-D score of ≥22 *vs.* <22); and drug-using behaviour in the past six months before baseline or a follow-up assessment, including heroin injection (≥daily *vs*. <daily), cannabis use (≥daily *vs*. <daily), cocaine/crack use (≥daily *vs*. <daily) and benzodiazepine use (yes *vs*. no).

We used an extended Cox model to examine bivariable and multivariable associations between the explanatory variables and the time to initiate heavy alcohol use. Age, MMT enrolment, HIV serostatus and all drug-using behaviour were treated as time-varying variables. To make sure that all these factors preceded the estimated initiation of heavy drinking, these time-varying variables were lagged by one follow-up assessment and referred to the six months prior to the follow-up questionnaire(s) up until one immediately preceding the first report of heavy drinking. All explanatory variables were included in the multivariable model. All *p*-values were two-sided. All statistical analyses were performed using the SAS software version 9.3 (SAS, Cary, NC, USA).

Results

A total of 357 participants were eligible for this analysis and followed for a median of 50.3 months (interquartile range [IQR]: 16.2–86.2). Of those, 251 (70%) were male, and 212 (59%) were Caucasian (Table 1). At baseline, 210 (59%) reported daily injection heroin use in the past six months and 180 (50%) had CES-D scores of ≥22. In total, 208 (58%) initiated MMT during follow-up. The groups in- and out- of the MMT were comparable at baseline, except for gender, depression, heroin, cannabis and cocaine/crack use. In the overall sample, a total of 115 (32%) people initiated heavy alcohol use for an incidence density of 7.8 events [95% confidence

interval (CI) = 6.4–9.5] per 100 person-years. Among those with no MMT enrolment throughout follow-up, the incidence density was 16.2 events (95% CI = 12.1–21.6) per 100 person-years, whereas it was 4.6 events (95% CI = 3.5–6.1) per 100 person-years among those reporting enrolment in MMT at least at one follow-up visit. The difference was statistically significant with p-value of <0.001.

<insert Table 1 here>

Table 2 below shows the results of bivariable and multivariable extended Cox regression analyses. As shown, MMT enrolment was not significantly associated with heavy drinking in bivariable (relative hazard = 1.26; 95% CI = 0.80 – 1.98) or multivariable analyses (adjusted relative hazard [ARH] = 1.27; 95% CI = 0.78 – 2.07). Age and cannabis use were the only variables that were independently associated with the time to onset of heavy drinking (ARH = 0.74; 95% CI = 0.58 – 0.94) and (ARH = 2.06; 95% CI = 1.32 – 3.19), respectively, after adjustment for relevant demographic and substance-use characteristics.

<insert Table 2 here>

Discussion

In this study, enrolment in MMT was not associated with heavy drinking among our cohort of people who used heroin. Previous studies have found mixed results regarding the substitution of one substance (heroin) for another (alcohol) upon enrolment in MMT. While some suggested that such substitution occurred, others did not [14,15,23]. One could speculate that the substitution hypothesis holds only for people who actively seek treatment, and, who therefore may have greater severity of health- or drug-related problems, including drinking. However, our findings suggest that it is younger age, rather than treatment seeking behaviour,

that may be associated with initiation of heavy drinking among people who use heroin. Inclusion into MMT may even decrease the initiation of heavy drinking. Such findings are consistent with previous research [24]. Although stimulants (cocaine), and other drugs, including cannabis and benzodiazepines, have been previously found to be potential predictors of changes in alcohol consumption [5], our research confirmed this for cannabis only. Irrespective of the reasons for heavy drinking, our study confirmed a high prevalence of this problem (32%); therefore, the national guidelines and policies should give clear guidance about the management of concurrent heavy drinking among this population. More research should be conducted to help inform decisions regarding strategies for addressing heavy drinking among people who use heroin, including screening, brief intervention, referral to treatment or medication assisted therapy, as be part of MMT.

We note several limitations of our research. First, our conclusions may not be generalizable, because our cohorts are non-randomized samples. Second, self-reported data may be subject to response bias, although the argument against the validity of such data has been shown to be overstated [25]. Third, similar to all observational studies, the relationships between the independent and outcome variables may be under the influence of unobserved confounding. Lastly, although we did not confirm the heavy drinking by objective measures, such as breath or urine ETG (Ethyl Glucuronide) tests, such measures detect recent drinking only and are not considered the gold standard without the complementary self-report methods [26,27]. Future research should also explore the contribution of HIV-related clinical characteristics to the relationship between drinking and opioid agonist treatment among PWID living with HIV.

In summary, we did not find that enrolment in MMT was associated with initiation of heavy alcohol use among people who used heroin, and who were not engaged in heavy alcohol

use, or enrolled in MMT, at baseline. The "substitution" controversy (alcohol for heroin) was not confirmed. Future prospective analyses should also examine the second key controversy in this field, that is, whether heavy drinking post-MMT leads to a relapse to one's primary drug problem.

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Table 1 Baseline characteristics stratified by those who accessed MMT at some point during follow-up vs. those who did not (n = 357)

Characteristic	Value	Total n (%) 357 (100)	Accessed MMT n (%) 208 (58)	Did not access MMT n (%) 149 (42)	P-value
Age (median, IQR)	Per 10 years older	40 (34-45)	39 (34-45)	41 (34-47)	0.343
Gender	Male	251 (70.3)	131 (63.0)	120 (80.5)	<0.001
	Female	106 (29.7)	77 (37.0)	29 (19.5)	
Ethnicity/Ancestry	Caucasian	212 (59.4)	125 (60.1)	87 (58.4)	0.059
	Aboriginal	116 (32.5)	72 (34.6)	44 (29.5)	
	Other	29 (8.1)	11 (5.3)	18 (12.1)	
CES-D	≥22	180 (50.4)	117 (56.3)	63 (42.3)	0.009
	<22	177 (49.6)	91 (43.8)	86 (57.7)	
Heroin injection[a]	≥Daily	210 (58.8)	139 (66.8)	71 (47.7)	<0.001
	<Daily	147 (41.2)	69 (33.2)	78 (52.3)	
Cannabis use[a]	≥Daily	66 (18.5)	28 (13.5)	38 (25.5)	0.004
	<Daily	290 (81.2)	179 (86.1)	111 (74.5)	
Cocaine/Crack cocaine use[a]	≥Daily	198 (55.5)	125 (60.1)	73 (49.0)	0.037
	<Daily	159 (44.5)	83 (39.9)	76 (51.0)	
Benzodiazepine use[a]	Yes	4 (1.1)	3 (1.4)	1 (0.7)	0.643
	No	353 (98.9)	205 (98.6)	148 (99.3)	
HIV serostatus	Positive	113 (31.7)	68 (32.7)	45 (30.2)	0.618
	Negative	244 (68.3)	140 (67.3)	104 (69.8)	

MMT= methadone maintenance therapy; CES-D= Center for Epidemiologic Studies Depression Scale

[a] Denotes activities in the previous 6 months.

Table 2: Bivariable and multivariable extended Cox regression analyses of factors associated with heavy drinking among people who use heroin in Vancouver, Canada (*n* = 357).

Characteristic	Relative Hazard (RH)			
	Unadjusted (95% CI)	*P*-value	Adjusted (95% CI)	*P*-value
Lagged MMT enrolment[a]				
(Yes *vs.* No)	1.26 (0.80 – 1.98)	0.327	1.27 (0.78 – 2.07)	0.340
Age				
(Per 10 years older)	0.75 (0.60 – 0.93)	0.010	0.74 (0.58 – 0.94)	0.012
Gender				
(Male *vs*. Female)	1.08 (0.73 – 1.61)	0.692	1.60 (1.01 – 2.52)	0.044
Ethnicity/Ancestry				
(Caucasian *vs*. Others)	0.68 (0.34 – 1.37)	0.278	0.76 (0.35 – 1.65)	0.486
(Aboriginal *vs*. Others)	1.15 (0.57 – 2.33)	0.698	1.47 (0.65 – 3.31)	0.357
Baseline depression				
(CES-D score of ≥22 *vs*. <22)	1.09 (0.76 – 1.57)	0.651	1.19 (0.81 – 1.74)	0.384
Lagged heroin injection[a]				
(≥Daily *vs.* <Daily)	0.65 (0.43 – 0.99)	0.046	0.72 (0.45 – 1.15)	0.172
Lagged cannabis use[a]				
(≥Daily *vs.* <Daily)	2.08 (1.35 – 3.19)	<0.001	2.06 (1.32 – 3.19)	0.001
Lagged cocaine/ Crack cocaine use[a]				
(≥Daily *vs.* <Daily)	0.86 (0.58 – 1.27)	0.445	0.85 (0.55 – 1.31)	0.464
Lagged benzodiazepine use[a]				
(Yes *vs*. No)	2.25 (0.54 – 9.45)	0.268	2.24 (0.54 – 9.32)	0.268
Lagged HIV status[a]				
(Positive vs. Negative)	0.98 (0.66 – 1.45)	0.911	0.93 (0.61 – 1.42)	0.743

CI= confidence interval; MMT= methadone maintenance therapy; CES-D= Center for Epidemiologic Studies Depression Scale

[a] All behavioural variables refer to the six months prior to the follow-up questionnaire immediately preceding the first report of heavy drinking.