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GENDER DIFFERENCES IN ACCESS TO METHADONE MAINTENANCE THERAPY IN A CANADIAN SETTING

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Abstract

Introduction and Aims—Methadone maintenance therapy (MMT) is an evidence-based treatment for opioid addiction. While gender differences in MMT pharmacokinetics, drug use patterns and clinical profiles have been previously described, few studies have compared rates of MMT use among community-recruited samples of persons who inject drugs (IDU).

Design and Methods—The present study used prospective cohorts of IDU followed between May 1996 and May 2013 in Vancouver, British Columbia, Canada. We investigated potential factors associated with time to methadone initiation using Cox proportional hazards modeling. Stratified analyses were used to examine for gender differences in rates of MMT enrolment.

Results—Overall, 1848 baseline methadone naïve IDU were included in the study, among whom 595 (32%) were female. In an adjusted model, male gender was independently associated with increased time to MMT initiation and an overall lower rate of enrolment (adjusted relative hazard (ARH) = 0.74 [95% confidence interval (CI): 0.65-0.85]). Among both female and male IDU, Caucasian ethnicity and daily injection heroin use were associated with decreased time to methadone initiation, while in females pregnancy was also associated with more rapid initiation.

Discussion and Conclusions—These data highlight gender differences in methadone use among a population of community-recruited IDU. While factors associated with methadone use were similar between genders, rates of use were lower among male IDU, highlighting the need to consider gender when designing strategies to improve recruitment into MMT.

Keywords

methadone; gender; intravenous drug abuse; MMT

INTRODUCTION

Methadone maintenance therapy (MMT) is an evidence-based approach for treating opioid addiction (1, 2). While its effectiveness in reducing heroin use has been clearly demonstrated, outstanding questions remain regarding the ability of MMT programs to attract and retain different populations of opioid addicted persons (3, 4). Variables associated with increased MMT initiation among females in past studies have included younger age at the time of starting MMT, less extensive criminal records, increased use of amphetamines, and decreased alcohol dependence as compared to their male counterparts (3, 5). Females also have higher rates of retention in MMT programs (6-8). In addition to differences in MMT uptake, gender differences have been noted in clinical presentation, drug use patterns, and co-morbidities of opioid-dependant patients, leading to the hypothesis that pathways to heroin use and long-term effects of heroin dependence may not be equivalent between genders (9-11).

Despite substantial evidence supporting the use of methadone for the treatment of opioid addiction, participation in MMT programs remains low in many settings (12, 13). A direct relationship between gender and MMT access has not previously been established, however gender-specific barriers to healthcare do exist and appear to be greater for women than for men (14, 15). In Canada, MMT is widely accessible via physician's offices, various health authorities, and other private services. Its provision is frequently supported by a universal healthcare system, reducing economic obstacles to treatment. Within British Columbia MMT is available with little wait time, and enrolment has been steadily increasing over the past 15 years (16). The present study was conducted to examine gender differences in MMT initiation among a community-recruited sample of persons who inject drugs (IDU).

METHODS

Our study was performed using data from the previously described Vancouver Injection Drug Users Study (VIDUS), a longstanding prospective cohort in the Downtown Eastside of Vancouver starting in 1996 (17), and the AIDS Care Cohort to Evaluate Access to Survival Services (ACCESS), a sister cohort of HIV-positive drug users started in 2005 (18). Briefly, individuals who use injection drugs were recruited and are followed on a semi-annual basis where they provide blood samples and respond to an interviewer-administered questionnaire. The cohorts use analogous recruitment, follow-up, and survey procedures to allow for merging of data. They receive annual approval from the University of British Columbia/ Providence Healthcare Research Ethics Board.

The present study was restricted to those IDU who were methadone naïve at study recruitment and completed at least one interview between May 1996 and May 2013. Our primary outcome of interest was time to MMT initiation, defined as the time interval between recruitment into the cohort and first starting methadone use. Our primary independent variable of interest was gender. Secondary variables examined included age, ethnicity (Caucasian vs. other), at least daily injection heroin use (yes vs. no), at least daily injection cocaine use (yes vs. no), at least daily crack cocaine smoking (yes vs. no), HIV status (positive vs. negative), hepatitis C (HCV) antibody status (positive vs. negative), sex

work involvement defined as exchanging sex for money, food, drugs, shelter or other commodities (yes vs. no), unstable housing defined as homelessness within the past 6 months (yes vs. no), current pregnancy (yes vs. no), and incarceration in the previous six months (yes vs. no). In order to protect against reverse causality and to control for methadone eligibility, daily injection heroin use was lagged to the previously completed questionnaire. Unless specified, all behavioural variables refer to activities taking place within the previous 6 months.

Initially, baseline demographics and behaviours between methadone-naïve male and female cohort members were compared using Pearson's chi-squared test for categorical variables and the Wilcoxon rank-sum test for continuous variables. Subsequently, we stratified by gender and estimated the cumulative incidence probabilities of time to MMT enrolment using Kaplan-Meier methods and the log-rank test.

Next, we used Cox proportional hazards analyses to identify the association between gender and time to methadone initiation. Potential confounders were examined in univariate Cox analyses. To fit the multivariate confounding model for the variable of interest, we employed a conservative model selection approach (19). Specifically, we fitted a full model with all potential confounders where $p < 0.05$ in the univariate analyses, then used a stepwise approach to fit a series of reduced models, dropping secondary variables with less relative influence on the relationship between the variable of interest and outcome. The final model was selected when the minimum relative change exceeded 5%. The remaining secondary variables were considered confounders in the multivariate analysis.

As a sub-analysis, a gender-stratified analysis was done to identify variables associated with methadone in males and females separately. As above, to fit the multivariate model for each sub-analysis we constructed a full model with all variables where $p < 0.05$ in the univariate analyses, then used a backward model selection process to obtain the model with the best overall fit as indicated by the lowest Akaike Information Criteria (AIC) value. All statistical analyses were performed using the SAS software version 9.3 (SAS, Cary, NC, USA). All p -values are two sided.

RESULTS

A total of 1848 participants were recruited during the study period, among whom 1253 (68%) were male and 595 (32%) were female. Non-Caucasians predominantly self-identified as Canadian Aboriginals (617 out of 818, 75%). At baseline, female participants were on average younger (median age: 31 years vs. 37 years, $p < 0.001$), more likely to be of non-Caucasian ethnicity (55% vs. 39%, $p < 0.001$), more likely to inject heroin (51% vs. 36%, $p < 0.001$) and/or cocaine (40% vs. 30%, $p < 0.001$) at least daily, more likely to smoke crack cocaine at least daily (28% vs. 19%, $p < 0.001$), and more likely to have had recent involvement in sex work (56% vs. 9%, $p < 0.001$). No statistical differences were seen in HIV and HCV status, stability of current housing, or recent incarceration (Table 1).

As shown in Figure 1, the Kaplan-Meier analysis of MMT initiation showed a significant difference in the cumulative incidence between males and females ($p < 0.001$). Similarly, in

the multivariate Cox model (Table 2), male gender remained independently associated with a prolonged time-to-methadone interval (adjusted hazard ratio [AHR]: 0.74 [95% confidence interval [CI]: 0.65-0.85]) (Table 2). When the analysis was stratified to consider factors associated with MMT initiation among men and women separately, we found that among women factors independently associated with initiating methadone included Caucasian ethnicity (AHR: 1.35 [95% CI: 1.10-1.66]), daily injection heroin use (AHR: 4.50 [95% CI: 3.40-5.95]), and current pregnancy (AHR: 2.31 [95% CI: 1.42-3.76]). Among males similar factors were also independently associated with MMT enrolment: Caucasian ethnicity (AHR: 1.56 [95% CI: 1.32-1.85]), and daily injection heroin use (AHR: 4.86 [95% CI: 3.98-5.94]). An analysis was conducted excluding individuals with a history of pregnancy and found that male gender remained associated with a slower rate of MMT uptake (AHR: 0.72 [95% CI: 0.63-0.83]).

DISCUSSION

Previous studies in other settings have demonstrated increased uptake and retention of female heroin users in MMT programs (6-8). Our study provides further evidence that female gender is a strong predictor of a shorter time to entry into MMT in a prospective cohort of Canadian IDU. The explanation for why this occurs is likely multifactorial as there are many unique bio-psycho-social factors that are specific to addiction among women. These have been previously described in a Canadian context, and include differences in drug use patterns, mental health co-morbidities, sexual abuse and violence histories, and parenthood (21). In addition, real or perceived side effects of MMT for males, such as sexual dysfunction, may play a role (20). Our observation that current pregnancy is associated with increased MMT enrolment is consistent with studies that describe it as a strong motivator for enrolment into drug treatment (22). Interestingly, it has recently been shown that HIV-positive females experience poorer quality of HIV care than their male counterparts in another Vancouver cohort with a high percentage of IDU (15). Given the similarities between these two female populations and the positive relationship between MMT and antiretroviral therapy (23, 24), the discordant results are surprising.

This study has several limitations, including the question of generalizability of our results given that it is not based on a random sample. The VIDUS and ACCESS cohorts are thought to be representative of Vancouver IDU, but how applicable these data are in other settings is uncertain. Furthermore, this study depends on self-reporting for variables such as methadone initiation, drug use patterns, sex work involvement, and housing situations that may be under- or over-reported. Lastly, comprehensive measurements of motherhood were not available in our data set.

CONCLUSIONS

In the present study we found gender differences in methadone use among a community-recruited sample of IDU. Though factors associated with methadone use were similar between genders, current pregnancy was associated with a significantly decreased time to MMT initiation, and male IDU did not access MMT as rapidly as their female counterparts. Given the consistency of these findings across other jurisdictions, our results reinforce the

differences in behaviour between genders in terms of accessing MMT, and highlight the need to consider gender when designing strategies to improve recruitment into MMT.

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REFERENCES

1. Faggiano F, Vigna-Taglianti F, Versino E, Lemma P. Methadone maintenance at different dosages for opioid dependence. The Cochrane database of systematic reviews. 2003; (3):CD002208. [PubMed: 12917925]
2. Mattick RP, Breen C, Kimber J, Davoli M. Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. The Cochrane database of systematic reviews. 2003; (2):CD002209. [PubMed: 12804430]
3. Chatham LR, Hiller ML, Rowan-Szal GA, Joe GW, Simpson DD. Gender differences at admission and follow-up in a sample of methadone maintenance clients. Substance use & misuse. 1999; 34(8): 1137–65. [PubMed: 10359226]
4. Craddock SG, Rounds-Bryant JL, Flynn PM, Hubbard RL. Characteristics and pretreatment behaviors of clients entering drug abuse treatment: 1969 to 1993. The American journal of drug and alcohol abuse. 1997; 23(1):43–59. [PubMed: 9048146]
5. Lin HC, Chang YP, Wang PW, Wu HC, Yen CN, Yeh YC, et al. Gender differences in heroin users receiving methadone maintenance therapy in Taiwan. Journal of addictive diseases. 2013; 32(2): 140–9. [PubMed: 23815421]
6. Deck D, Carlson MJ. Retention in publicly funded methadone maintenance treatment in two Western States. The journal of behavioral health services & research. 2005; 32(1):43–60. [PubMed: 15632797]
7. Kelly SM, O'Grady KE, Mitchell SG, Brown BS, Schwartz RP. Predictors of methadone treatment retention from a multi-site study: a survival analysis. Drug Alcohol Depend. 2011; 117(2-3):170–5. [PubMed: 21310552]
8. Mullen L, Barry J, Long J, Keenan E, Mulholland D, Grogan L, et al. A national study of the retention of Irish opiate users in methadone substitution treatment. The American journal of drug and alcohol abuse. 2012; 38(6):551–8. [PubMed: 22747484]
9. Back SE, Payne RL, Wahlquist AH, Carter RE, Stroud Z, Haynes L, et al. Comparative profiles of men and women with opioid dependence: results from a national multisite effectiveness trial. The American journal of drug and alcohol abuse. 2011; 37(5):313–23. [PubMed: 21854273]
10. Ross J, Teesson M, Darke S, Lynskey M, Ali R, Ritter A, et al. The characteristics of heroin users entering treatment: findings from the Australian treatment outcome study (ATOS). Drug and alcohol review. 2005; 24(5):411–8. [PubMed: 16298835]
11. Shand FL, Degenhardt L, Slade T, Nelson EC. Sex differences amongst dependent heroin users: histories, clinical characteristics and predictors of other substance dependence. Addictive behaviors. 2011; 36(1-2):27–36. [PubMed: 20833480]
12. Bobrova N, Rughnikov U, Neifeld E, Rhodes T, Alcorn R, Kirichenko S, et al. Challenges in providing drug user treatment services in Russia: providers' views. Substance use & misuse. 2008; 43(12-13):1770–84. [PubMed: 19016164]
13. Sarang A, Stuijke R, Bykov R. Implementation of harm reduction in Central and Eastern Europe and Central Asia. Int J Drug Policy. 2007; 18(2):129–35. [PubMed: 17689355]
14. Baghdadi G. Gender and medicines: an international public health perspective. Journal of women's health. 2005; 14(1):82–6.

15. Carter A, Eun Min J, Chau W, Lima VD, Kestler M, Pick N, et al. Gender inequities in quality of care among HIV-positive individuals initiating antiretroviral treatment in British Columbia, Canada (2000-2010). *PloS one*. 2014; 9(3):e92334. [PubMed: 24642949]
16. Urban Health Research Initiative BCCfEiHA. Drug Situation in Vancouver. 2013
17. Strathdee SA, Patrick DM, Currie SL, Cornelisse PG, Rekart ML, Montaner JS, et al. Needle exchange is not enough: lessons from the Vancouver injecting drug use study. *AIDS*. 1997; 11(8):F59-65. [PubMed: 9223727]
18. Palepu A, Tyndall MW, Joy R, Kerr T, Wood E, Press N, et al. Antiretroviral adherence and HIV treatment outcomes among HIV/HCV co-infected injection drug users: the role of methadone maintenance therapy. *Drug Alcohol Depend*. 2006; 84(2):188-94. [PubMed: 16542797]
19. Maldonado G, Greenland S. Simulation study of confounder-selection strategies. *American journal of epidemiology*. 1993; 138(11):923-36. [PubMed: 8256780]
20. Yee A, Loh HS, Hisham Hashim HM, Ng CG. The prevalence of sexual dysfunction among male patients on methadone and buprenorphine treatments: a meta-analysis study. *The journal of sexual medicine*. 2014; 11(1):22-32. [PubMed: 24344738]
21. Poole, N., Greaves, L. *Highs & Lows: Canadian Perspectives on Women and Substance Use*. CAMH; Toronto: 2007.
22. Mitchell MM, Severtson SG, Latimer WW. Pregnancy and race/ethnicity as predictors of motivation for drug treatment. *The American journal of drug and alcohol abuse*. 2008; 34(4):397-404. [PubMed: 18584569]
23. Reddon H, Milloy MJ, Simo A, Montaner J, Wood E, Kerr T. Methadone Maintenance Therapy Decreases the Rate of Antiretroviral Therapy Discontinuation Among HIV-Positive Illicit Drug Users. *AIDS and behavior*. 2014; 18(4):740-6. [PubMed: 23918244]
24. Uhlmann S, Milloy MJ, Kerr T, Zhang R, Guillemi S, Marsh D, et al. Methadone maintenance therapy promotes initiation of antiretroviral therapy among injection drug users. *Addiction*. 2010; 105(5):907-13. [PubMed: 20331553]

Figure 1.
Cumulative incidence probability curve of time to MMT initiation by gender.

Table 1

Baseline demographics of analytic sample stratified by gender (n=1848).

Variable	Male (%) 1253 (68%)	Female (%) 595 (32%)	p-value £
Age (in years)			
Median (IQR [*])	37 (30 – 44)	31 (24 – 39)	<0.001
Caucasian ethnicity			
No	493 (39)	325 (55)	<0.001
Yes	760 (61)	270 (45)	
Daily injection heroin use [†]			
No	798 (64)	293 (49)	<0.001
Yes	453 (36)	301 (51)	
Daily injection cocaine use [†]			
No	865 (69)	352 (59)	<0.001
Yes	380 (30)	239 (40)	
Daily crack smoking [†]			
No	1016 (81)	428 (72)	<0.001
Yes	237 (19)	165 (28)	
HIV positive			
No	903 (72)	431 (72)	0.868
Yes	350 (28)	164 (28)	
HCV positive			
No	229 (18)	106 (18)	0.843
Yes	1019 (81)	484 (81)	
Sex work [†]			
No	1142 (91)	257 (43)	<0.001
Yes	110 (9)	336 (56)	
Unstable housing [‡]			
No	356 (28)	174 (29)	0.699
Yes	886 (71)	415 (70)	
Recent incarceration [†]			
No	1080 (86)	516 (87)	0.757
Yes	173 (14)	79 (13)	

£ Note: Results based on the Pearson's Chi-square test for categorical variables and the Mann-Whitney test for continuous variables.

* IQR = Interquartile range.

[†] Denotes activities or situations referring to the previous 6 months.

[‡] Denotes current activities. Percentages may not sum up to 100% due to missing data and/or rounding error.

Table 2

Univariate and multivariate Cox analyses of the time to methadone initiation among injection drug users in Vancouver, Canada.

Variable	Unadjusted Relative Hazard (RH)			Adjusted Relative Hazard (RH)		
	RH	95% CI*	p-value	RH	95% CI*	p-value
Gender						
(male vs. female)	0.64	0.56 – 0.73	<0.001	0.74	0.65 – 0.85	<0.001
Age						
(per 10-year increase)	0.81	0.75 – 0.86	<0.001	--	--	--
Caucasian ethnicity						
(yes vs. no)	1.47	1.29 – 1.68	<0.001	1.42	1.25 – 1.62	<0.001
Daily injection heroin use †						
(yes vs. no)	4.96	4.25 – 5.78	<0.001	4.77	4.07 – 5.58	<0.001
Daily injection cocaine use †						
(yes vs. no)	1.30	1.11 – 1.52	0.001	--	--	--
Daily crack smoking †						
(yes vs. no)	1.40	1.21 – 1.61	<0.001	--	--	--
HIV status						
(positive vs. negative)	0.93	0.80 – 1.07	0.309	--	--	--
HCV status						
(positive vs. negative)	1.30	1.03 – 1.64	0.026	--	--	--
Sex work †						
(yes vs. no)	1.51	1.28 – 1.80	<0.001	--	--	--
Unstable housing ‡						
(yes vs. no)	1.25	1.09 – 1.43	0.002	--	--	--
Recent incarceration †						
(yes vs. no)	1.18	1.02 – 1.37	0.027	--	--	--

* Note: CI = Confidence interval.

† Denotes activities or situations referring to previous 6 months.

‡ Denotes current activities.