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The impact of low-threshold methadone maintenance treatment on mortality in a Canadian setting

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ABSTRACT

Background: Methadone maintenance therapy (MMT) is among the most effective treatment modalities available for the management of opioid use disorder. However, the effect of MMT on mortality, and optimal strategies for delivering methadone are less clear. This study sought to estimate the effect of low-threshold MMT and its association with all-cause mortality among persons who inject drugs (PWID) in a setting where methadone is widely available through primary care physicians and community pharmacies at no cost through the setting's universal medical insurance plan.
Methods: Between May, 1996 and December, 2011 data were collected as part of two prospective cohort studies of PWID in Vancouver, Canada, and were linked to the provincial vital statistics database to ascertain rates and causes of death. The association of MMT with all-cause mortality was estimated using multivariable extended Cox regression with time-dependent variables.
Results: Of 2335 PWID providing 15027 person-years of observation, 511 deaths were observed for a mortality rate of 3.4 (95% Confidence Interval [CI]: 3.1–3.7) deaths per 100 person-years. After adjusting for potential confounders including age and HIV seropositivity, MMT enrolment was found to be associated with lower mortality (adjusted hazard ratio [AHR] = 0.73, 95% CI: 0.61–0.88).
Conclusions: While observed all-cause mortality rates among PWID in this setting were high, participation in low-threshold MMT was significantly associated with improved survival. These findings add to the known benefits of providing low-threshold MMT on reducing the harms associated with injection drug use.

1. Introduction

In North America, the use of prescription and illicit opioids continues to increase with devastating consequences (Goodnough, 2015). Opioid dependence has become a serious public health concern as a result of these growing trends (Fullerton et al., 2014; King et al., 2014). Without treatment, the risk of premature death amongst illicit opioid users is significant with estimates ranging from 13 to 63 times higher than that of the general population (English et al., 1995; Gronbladh et al., 1990; Hulse et al., 1999).

While the benefits of methadone maintenance therapy (MMT) for the reduction of illicit opioid use and retention in treatment are well established, its effect on mortality is less clear. Several randomized controlled trials (Gunne and Gronbladh, 1981; Kinlock et al., 2007; Newman and Whitehill, 1979; Yancovitz et al., 1991) comparing MMT and non-pharmacological options were included in a 2009 Cochrane review; separately or pooled, they showed no significant difference in mortality (Mattick et al., 2009). These results are difficult to interpret, however, as the included studies had small sample sizes and low mortality rates. A number of observational and registry studies have demonstrated an association between methadone use and reduced mortality (Bell et al., 2009; Clausen et al., 2008; Degenhardt et al., 2009; Evans et al., 2015; Gibson et al., 2008). A 2008 Norwegian prospective, cross-registry study (Clausen et al., 2008) following 3789 opioid dependent patients who applied for opioid maintenance therapy (OMT) demonstrated a reduction in mortality using an intention to treat analysis (relative risk = 0.60, $p = 0.004$). Through data linkage, an Australian study by Degenhardt et al., in 2009 demonstrated an overall 29% reduction in mortality among 42,676 opioid-dependent

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participants entering OMT between 1985 and 2006. Lastly, a more recent longitudinal study published by Evans et al., in 2015 assessed mortality among opioid dependent individuals accessing MMT in the U.S. between 2006 and 2010 and found a decrease in mortality risk with MMT (hazard ratio = 0.30, 95% confidence interval [CI]: 0.25–0.37).

While these studies do demonstrate an association between MMT participation and improved mortality, the strength of this association may be understated given the comparison group is often in receipt of psychosocial treatments and those receiving no treatment are excluded. Often programmatic barriers such as limiting MMT administration to specialized clinics, long-wait lists for treatment entry and lack of universal medical insurance coverage restrict access to MMT (Peterson et al., 2010). Furthermore even when opioid users have access to MMT, limits on dosing and duration of maintenance may limit its potential (Strain et al., 1999). British Columbia, Canada, is a unique environment that overcomes these challenges as the provision of MMT always occurs through a low-threshold methadone program. Specifically, MMT is widely accessible through the setting's universal no-cost medical insurance plan and through the integration of prescribing and dispensation through community physicians and community pharmacies respectively (Nosyk et al., 2012). Furthermore, low-threshold methadone administration occurs without any restriction on the maximum dose needed for desired efficacy or duration of treatment and while abstinence is the ultimate goal, it is not a prerequisite for continuation with the program. Thus, in this setting we sought to determine the relationship between MMT enrolment and all-cause mortality amongst persons who inject drugs (PWID) over a 15 year follow-up period.

2. Materials and methods

2.1. Study population

The present study derived data from the Vancouver Injection Drug Users Study (VIDUS) and the AIDS Care Cohort to Evaluate Access to Survival Services (ACCESS); two open prospective cohort studies of illicit drug users in Vancouver, British Columbia, Canada. Described in detail previously (Palepu et al., 2006; Strathdee et al., 1998), ACCESS and VIDUS comprise of HIV-positive and HIV-negative participants respectively. Beyond this, both cohorts follow identical recruitment and follow up procedures to allow for the analyses of merged data, with the only differences being that HIV-positive individuals are followed in ACCESS, HIV-negative individuals are followed in VIDUS and that ACCESS includes a small number of non-injecting (e.g., crack cocaine) drug users. Enrollment for both cohorts began in 1996 through extensive street outreach and self-referral. Participants were eligible for inclusion if they were aged ≥18 years, reported using an illicit drug other than cannabis at least once in the preceding month (for ACCESS) or injecting a drug at least once in the past month (for VIDUS), resided in the greater Vancouver region at the time of enrolment and provided written informed consent.

2.2. Study assessments

At baseline and semiannually, participants completed an interviewer-administered questionnaire and provided a blood sample for HIV and hepatitis C antibody testing, and HIV-positive individuals are further assessed for HIV disease progression and antiretroviral resistance. Detailed data on sociodemographic characteristics, drug use patterns, risk behaviors and status of active participation in an MMT program were solicited. Participants were provided with basic medical care and, where appropriate, were referred to additional health care services. They also received a $20 honorarium after each study visit for compensation. The VIDUS and ACCESS cohorts have been approved by the University of British Columbia/Providence Health Care research ethics board.

2.3. Measures

All cohort participants who had a history of injection drug use at baseline and who were recruited between May 1996 and December 2011 were eligible for inclusion. The primary outcome was all-cause mortality determined through a confidential record linkage with the British Columbia Vital Statistics Agency, in addition to ongoing follow up with contacts provided by the participants. Cause of death was recorded in the Vital Statistics database according to the International Classification of Diseases, both 9th and 10th editions.

Follow-up time was calculated from the date of initial study enrollment to the date of either the last study visit (non-deceased) or the date of death (deceased). To avoid potential bias relating to long durations between the last study visit where behavioral information was assessed and the date of death (i.e., loss to regular follow-up), individuals who were identified as deceased more than 24 months after the last follow-up visit were censored on the date of the last follow-up visit. Sensitivity analyses were also conducted whereby we included the entire sample without this censoring process in effect. We also conducted sub-analyses restricted to overdose and non-overdose related mortality.

The primary endpoint in this analysis was time to all-cause mortality. The crude mortality rate and 95% confidence interval were calculated using Poisson regression. The exposure of interest was enrollment in MMT (yes vs. no), which was time updated at each six month assessment based on self-report of any methadone prescription in the preceding six months. Several time-dependent, secondary explanatory variables of interest were measured at baseline and repeatedly during each semiannual follow-up visit and included: substance-use related behaviors (≥daily heroin injection [yes vs. no], ≥daily cocaine injection [yes vs. no], ≥daily crack cocaine smoking [yes vs. no]), HIV infection (yes vs. no), homelessness (yes vs. no), unstable housing (yes vs. no) and sex work involvement (yes vs. no). Unstable housing was defined as living in a single room occupancy hotel, a shelter or other transitional housing, or living on the street (Daly, 1996). Sex-work involvement was defined as exchanging sex for gifts, food, shelter, clothes, etc. (Miller et al., 2002). Other potential confounders considered included gender (male vs. female), age (per 10 years older), ethnicity (Caucasian vs. non-Caucasian), and years since first injection (per year longer).

2.4. Statistical analyses

First we used the Chi-square test and Wilcoxon rank sum test to compare the baseline characteristics of those who did and did not report enrollment in MMT at the initial study visit. The odds ratio and 95% confidence interval were calculated using logistic regression. Next, extended Cox regression (Kleinbaum and Klein, 1996), which can incorporate time-dependent variables with the counting process data format, was used to examine the bivariable relationship between each explanatory variable and time to all-cause mortality. Time-invariant potential confounders assessed at baseline included: gender, ethnicity and years since first injection. All behavioral, social and structural-level potential confounders were treated as time-dependents. To fit the multivariable confounder model, we employed a conservative stepwise backward selection approach previously described by Maldonado and Greenland (1993) and Rothman et al. (2008). We included all variables found to be associated with time to all-cause mortality in bivariable analyses in a full model. We then used a stepwise approach to fit a series of reduced models (Lima and Kopec, 2005). After comparing the value of the coefficient associated with enrollment in MMT in the full model to the value of the coefficient in each of the reduced models, we dropped the secondary variable associated with the smallest relative change. We continued this iterative process until the minimum change exceeded 5%. Remaining variables were considered as potential confounders in a final multivariable model. All statistical analyses were performed using SAS software version 9.3 (SAS, Cary, NC). All p-values were two-sided.

3. Results

Between May, 1996 and December, 2011, a total of 2595 PWID were recruited. Overall, 2335 (90.0%) participants were included in the study and 260 (10.0%) were excluded as a result of having no follow-up visit (and no confirmed death date) within 24 months of their baseline visit. Compared to the 260 (10.0%) individuals who were excluded, the participants included in these analyses were more likely to be younger, HIV negative or homeless in the preceding 6 months at baseline and were less likely to inject cocaine at least once daily (all $p < 0.05$). Furthermore, those excluded had a shorter median time since first injection (8.7 vs. 14.4 years, $p < 0.001$). There was no significant difference in MMT use at baseline between the groups ($p = 0.067$).

The 2335 participants included in this study were followed for a median of 60.7 months (25th–75th percentile [Q1–Q3] = 33.0–111.6) and provided 15,027 person-years of follow-up. Per participant, the median number of follow-ups was 8 ([Q1–Q3] = 4–15). Baseline characteristics of the study sample are shown in Table 1. Overall, 1556 (66.6%) were male, 642 (27.5%) were HIV-positive at baseline, 1430 (61.2%) were self-reported Caucasian ethnicity and 531 (22.7%) individuals were on MMT at baseline. The median age was 37.3 years (Q1–Q3 = 29.4–43.7) and the median time since first injection was 14.4 years (Q1–Q3: 6.2–24.2).