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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 timedependent 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).

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All other authors declare no competing interests.

Contributors:
Seonaid Nolan and Evan Wood designed and prepared the first draft of the manuscript. Vivianne Dias Lima and Huiru Dong conducted the statistical analyses. All coauthors contributed to the drafting of the final manuscript.

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.

Keywords

methadone; opioid maintenance treatment; MMT; mortality; death; 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 nonpharmacological 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 3,789 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 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 nonoverdose 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 and Greenland (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 (25^{th} – 75^{th} 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).

Compared to those not on MMT at baseline, those on MMT were less likely to be male, were more likely to be older, to report Caucasian ancestry, to have a longer time since first injection, to report ≥daily crack cocaine smoking and to be HIV-positive (all $p < 0.05$). Housing status (current unstable housing or recent homelessness) showed no statistically significant difference at baseline.

Overall, 511 (21.9%) participants died during follow-up, giving a mortality rate of 3.4 deaths (95% CI: 3.1 – 3.7) per 100 person-years. During follow-up, among the 1795 participants who were not on MMT at baseline, 834 (46.5%) individuals initiated MMT and the median number of 6-month intervals where MMT use was reported was 6 (Q1 – Q3 = 2 – 12). The mortality rate for participants who ever enrolled in MMT during the study period was 2.6 (95% CI: 2.3 – 2.9) deaths per 100 person-years. In comparison the mortality rate among those who never enrolled in MMT during the study period was 4.9 (95% CI: 4.3 – 5.5) deaths per 100 person-years. Table 2 shows results of the bivariable and multivariable Cox regression analyses of all-cause mortality. As can be seen, enrollment in MMT had a statistically significant protective association against time to all-cause mortality in the bivariable analyses (hazard ratio [HR]: 0.84, 95% CI: 0.70 – 0.99). The association remained statistically significant in each intermediate model of the step-wise process and in the final multivariable analyses (adjusted hazard ratio [AHR]: 0.73, 95% CI: 0.61 – 0.88) even after adjusting for confounders including age, HIV infection and daily heroin injection. In sensitivity analysis, where the entire sample was included without censoring, our results again showed the protective association of MMT against time to all-cause mortality in both

the bivariable and multivariable analyses (AHR: 0.82, 95% CI: 0.70 – 0.97, AHR: 0.73, 95% CI: 0.61 – 0.87 respectively). Additional sub-analyses also demonstrated that participation in a MMT program in the preceding six months was protective against non-overdose mortality (AHR: 0.72, 95% CI: 0.58 – 0.89) but the results for overdose mortality were not significant (ARH: 0.78, 95% CI: 0.55 – 1.12).

4. DISCUSSION

In the present study, we observed a high mortality rate among PWID in our setting. At the same time, we found that enrollment in a low-threshold MMT program was associated with a protective effect against all-cause mortality, even after adjusting for confounders including age, HIV infection and heroin injection.

Though many previous reports demonstrate the increased mortality risk faced by those with an opioid use disorder (English et al., 1995; Gronbladh et al., 1990; Evans et al., 2015; Hulse et al, 1999), studies designed specifically to assess the effect of MMT on mortality are less abundant. As stated previously, a 2009 Cochrane meta-analysis (Mattick et al., 2009) was only able to identify four randomized controlled trials that examined the impact of MMT on mortality. While the pooled effect did not reach statistical significance, individual studies did suggest a benefit. Subsequent to this study Fullerton et al. (2014) reviewed meta-analyses, systematic reviews and individual studies of MMT between 1995 and 2012. While the use of MMT did suggest a reduction in mortality, the evidence again remained inconclusive. Several observational studies previously described have demonstrated an association with MMT and a reduction in mortality. The most recent, a population based cohort study published in 2015, did demonstrate a significant reduction in mortality risk with the use of MMT alone (HR = 0.30, 95% CI: 0.25–0.37) and MMT with detoxification prior (HR = 0.20, 95% CI: 0.14–0.28) among opioid dependent individuals accessing pharmacotherapy. This inconsistency may be explained by the small sample sizes (n = 34 – 301) and short follow up periods (1 month – 7 years) of the studies included in the Cochrane meta-analysis, neither being ideal for accurately recording drug overdose events which constitute the majority of drug-related mortality (Gunne and Gronbladh, 1981; Kinlock et al., 2007; Newman and Whitehill, 1979; Yancovitz et al., 1991). Too few observed events might have impaired the ability to reach adequate statistical power and accurately study the effect of MMT on mortality in the combined meta-analysis. Furthermore, many of these studies included only those opioid dependent individuals who were seeking treatment, or were conducted in settings where methadone was available only at designated methadone clinics and may differ in the way in which the medication was provided. The present study was conducted among a large community-recruited cohort, over a long follow up period, in a setting where access to MMT is less restricted as it is free of charge, and is available for prescription from office practices and dispensed through community pharmacies (Nosyk et al., 2012).

The benefits of low-threshold MMT have previously been described (Carrieri et al., 2014; MacGowan et al., 1996; Novick et al., 1994; Weinrich and Stuart, 2000; Wittchen et al., 2008). More specifically, integrating the provision of MMT with primary care services results in improved treatment retention (MacGowan et al., 1996; Novick et al., 1994), an

improved ability to treat concurrent medical comorbidities (Weinrich and Stuart, 2000) and better geographic access to the medication itself (Weinrich and Stuart, 2000) when compared with specialized MMT clinics. Furthermore, patients with an opioid use disorder receiving MMT through this integrated treatment approach are more likely to accept treatment, report greater overall satisfaction (Carrieri et al., 2014), show improved health outcomes and demonstrate a significantly higher reduction in criminal activity (Wittchen et al., 2008) when compared with those receiving care from specialized MMT clinics. Given the ongoing challenges associated with opioid use and overdose in the U.S. and other settings, there is a continued need to expand access to methadone through various low-threshold means.

Our study has limitations. First, as is the case with other cohort studies of PWID, our sample was not recruited at random and thus the generalizability of these results to other drug-using populations is uncertain. Furthermore, our analyses were limited to include only PWID and thus may not be entirely representative of all opioid users. Secondly, given the observational nature of this study, causation cannot be inferred, as we cannot rule out unmeasured confounders. In this respect, we note that it would no longer be ethical to randomize active heroin users to receipt versus non-receipt of methadone for a study evaluating mortality. Thirdly, the potential for mismatch between our exposure (MMT enrollment) and outcome of interest (mortality) does exist as a significant time lag may have occurred between MMT enrollment, which relied on retrospective 6-month self-report, and mortality up to 24 months later. Nevertheless, MMT use was treated as a time updated variable based on assessment at each semi-annual follow up visit. As our exposure was binary in nature (ie. yes vs. no) we also were not able to capture number or duration of treatment episodes in the preceding 6-months nor rates of premature treatment discontinuation, all of which are known to have a potential impact on mortality. Despite this, however, our results remained statistically significant. Given the known increased mortality risk associated with the initial period of induction on methadone maintenance therapy (Baxter et al., 2013; Buster et al., 2002; Srivastava and Kahan, 2006) and our inclusion of this in our analyses, it is possible that the strength of the association between methadone use and reduced mortality observed in this study may be even stronger than reported here. Lastly, this study was based on self-report of behaviors of a criminalized and socially sensitive nature and therefore may be subject to social desirability or recall bias. However, we note that this type of data has been commonly utilized in studies involving PWID, and has been found to be valid (Darke, 1998).

In conclusion, we found participation in a program of low-threshold MMT to be strongly associated with a reduction in mortality amongst two long-standing cohorts of PWID in a Canadian setting. Given the evidence regarding the benefits of low-threshold MMT programs (Carrieri et al., 2014; MacGowan et al., 1996; Novick et al., 1994; Weinrich and Stuart, 2000; Wittchen et al., 2008), these findings further expand upon the known benefits of MMT for reducing the harms associated with injection drug use and support the need for universal and unrestricted access to low-threshold MMT for the treatment of opioid use disorder.

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REFERENCES

Baxter LE Sr, Campbell A, Deshields M, Levounis P, Martin JA, McNicholas L, Payte JT, Salsitz EA, Taylor T, Wilford BB. Safe methadone induction and stabilization: a report of an expert panel. J. Addict. Med. 2013; 7:377–386. [PubMed: 24189172]

Bell J, Trinh L, Butler B, Randall D, Rubin G. Comparing retention in treatment and mortality in people after initial entry to methadone and buprenorphine treatment. Addiction. 2009; 104:1193–1200. [PubMed: 19563562]

Buster MC, van Brussel GH, van den Brink W. An increase in overdose mortality during the first 2 weeks after entering or re-entering methadone treatment in Amsterdam. Addiction. 2002; 97:993–1001. [PubMed: 12144602]

Carrieri PM, Michel L, Lions C, Cohen J, Vray M, Mora M, Marcellin F, Spire B, Morel A, Roux P. Methadone induction in primary care for opioid dependence: a pragmatic randomized trial (ANRS Methaville). PLoS ONE. 2014; 9:e112328. [PubMed: 25393311]

Clausen T, Anchersen K, Waal H. Mortality prior to, during and after opioid maintenance treatment (OMT): a national prospective cross-registry study. Drug Alcohol Depend. 2008; 94:151–157. [PubMed: 18155364]

Daly, GP. Homeless: Policies, Strategies, And Lives On The Street. London: Routledge; 1996.

Darke S. Self-report among injecting drug users: a review. Drug Alcohol Depend. 1998; 51:253–263. discussion 267–268. [PubMed: 9787998]

Degenhardt L, Randall D, Hall W, Law M, Butler T, Burns L. Mortality among clients of a state-wide opioid pharmacotherapy program over 20 years: risk factors and lives saved. Drug Alcohol Depend. 2009; 105:9–15. [PubMed: 19608355]

English, DR.; Holman, CDJ.; Milne, E.; Winter, MG.; Hulse, GK.; Codde, JP.; Bower, CI.; Corti, B.; De Klerk, N.; Knuiman, MW.; Kurinczuk, JJ.; Lewin, GF.; Ryan, GA. The Quantification of Drug Caused Morbidity and Mortality in Australia 1995, Part 1, Alcohol. Canberra: Australian Government Publishing Service; 1995.

Evans E, Li L, Min J, Huang D, Urada D, Liu L, Hser YI, Nosyk B. Mortality among individuals accessing pharmacological treatment for opioid dependence in California, 2006–10. Addiction. 2015; 110:996–1005. [PubMed: 25644938]

Fullerton CA, Kim M, Thomas CP, Lyman DR, Montejano LB, Dougherty RH, Daniels AS, Ghose SS, Delphin-Rittmon ME. Medication-assisted treatment with methadone: assessing the evidence. Psychiatr. Serv. 2014; 65:146–157. [PubMed: 24248468]

Gibson A, Degenhardt L, Mattick RP, Ali R, White J, O'Brien S. Exposure to opioid maintenance treatment reduces long-term mortality. Addiction. 2008; 103:462–468. [PubMed: 18190664]

Goodnough A. An outbreak fed by misinformation and fear. N. Y. Times. Sect A. 2015 May 6.1

Gronbladh L, Ohlund LS, Gunne LM. Mortality in heroin addiction: impact of methadone treatment. Acta. Psychiatr. Scand. 1990; 82:223–227. [PubMed: 2248048]

Gunne LM, Gronbladh L. The Swedish methadone maintenance program: a controlled study. Drug Alcohol Depend. 1981; 7:249–256. [PubMed: 7261900]

Hulse GK, English DR, Milne E, Holman CD. The quantification of mortality resulting from the regular use of illicit opiates. Addiction. 1999; 94:221–229. [PubMed: 10396790]

King NB, Fraser V, Boikos C, Richardson R, Harper S. Determinants of increased opioid-related mortality in the United States and Canada, 1990–2013: a systematic review. Am. J. Public Health. 2014; 104:e32–e42. [PubMed: 24922138]

Kinlock TW, Gordon MS, Schwartz RP, O'Grady K, Fitzgerald TT, Wilson M. A randomized clinical trial of methadone maintenance for prisoners: results at 1-month post-release. Drug Alcohol Depend. 2007; 91:220–227. [PubMed: 17628351]

Kleinbaum, DG.; Klein, M. Survival Analysis. New York: Springer; 1996. p. 244-277.

Lima VD, Kopec JA. Quantifying the effect of health status on health care utilization using a preference-based health measure. Soc. Sci. Med. 2005; 60:515–524. [PubMed: 15550300]

MacGowan RJ, Swanson NM, Brackbill RM, Rugg DL, Barker T, Molde S. Retention in methadone maintenance treatment programs, Connecticut and Massachusetts, 1990–1993. J. Psychoactive Drugs. 1996; 28:259–265. [PubMed: 8895111]

Maldonado G, Greenland S. Simulation study of confounder-selection strategies. Am. J. Epidemiol. 1993; 138:923–936. [PubMed: 8256780]

Mattick RP, Breen C, Kimber J, Davoli M. Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. Cochrane Database Syst. Rev. 2009:CD002209. [PubMed: 19588333]

Miller CL, Johnston C, Spittal PM, Li K, Laliberte N, Montaner JS, Schechter MT. Opportunities for prevention: hepatitis c prevalence and incidence in a cohort of young injection drug users. Hepatology. 2002; 36:737–742. [PubMed: 12198668]

Newman RG, Whitehill WB. Double-blind comparison of methadone and placebo maintenance treatments of narcotic addicts in Hong Kong. Lancet. 1979; 2:485–488. [PubMed: 90214]

Nosyk B, Sun H, Evans E, Marsh DC, Anglin MD, Hser YI, Anis AH. Defining dosing pattern characteristics of successful tapers following methadone maintenance treatment: results from a population-based retrospective cohort study. Addiction. 2012; 107:1621–1629. [PubMed: 22385013]

Novick DM, Joseph H, Salsitz EA, Kalin MF, Keefe JB, Miller EL, Richman BL. Outcomes of treatment of socially rehabilitated methadone maintenance patients in physicians' offices (medical maintenance): follow-up at three and a half to nine and a fourth years. J. Gen. Intern. Med. 1994; 9:127–130. [PubMed: 8195910]

Palepu A, Tyndall MW, Joy R, Kerr T, Wood E, Press N, Hogg RS, Montaner JSG. Antiretroviral adherence and HIV treatment outcomes among HIV/HCV co-infected injection drug users: the role of methadone maintenance therapy. Drug Alcohol Depend. 2006; 84:188–194. [PubMed: 16542797]

Peterson JA, Schwartz RP, Mitchell SG, Reisinger HS, Kelly SM, O'Grady KE, Brown BS, Agar MH. Why don't out-of-treatment individuals enter methadone treatment programmes? Int. J. Drug Policy. 2010; 21:36–42. [PubMed: 18805686]

Rothman, KJ.; Greenland, S.; Lash, TL. Modern Epidemiology. 3rd ed.. Philadelphia: Lippincott Williams & Wilkins; 2008.

Strain EC, Bigelow GE, Liebson IA, Stitzer ML. Moderate- vs high-dose methadone in the treatment of opioid dependence: a randomized trial. JAMA. 1999; 281:1000–1005. [PubMed: 10086434]

Strathdee SA, Palepu A, Cornelisse PG, Yip B, O'Shaughnessy MV, Montaner JS, Schechter MT, Hogg RS. Barriers to use of free antiretroviral therapy in injection drug users. JAMA. 1998; 280:547–549. [PubMed: 9707146]

Srivastava A, Kahan M. Methadone induction doses: are current practices safe? J. Addict. Dis. 2006; 25:5–13. [PubMed: 16956864]

Weinrich M, Stuart M. Provision of methadone treatment in primary care medical practices: review of the Scottish experience and implications for US policy. JAMA. 2000; 283:1343–1348. [PubMed: 10714738]

Wittchen HU, Apelt SM, Soyka M, Gastpar M, Backmund M, Golz J, Kraus MR, Tretter F, Schafer M, Siegert J, Scherbaum N, Rehm J, Buhringer G. Feasibility and outcome of substitution treatment of heroin-dependent patients in specialized substitution centers and primary care facilities in Germany: a naturalistic study in 2694 patients. Drug Alcohol Depend. 2008; 95:245–257. [PubMed: 18337025]

Yancovitz SR, Des Jarlais DC, Peyser NP, Drew E, Friedmann P, Trigg HL, Robinson JW. A randomized trial of an interim methadone maintenance clinic. Am. J. Public Health. 1991; 81:1185–1191. [PubMed: 1659236]

Highlights

- 2335 persons who inject drugs (PWID) were followed over a 15 year follow up period
- 511 (21.9%) participants died (mortality ratio of 3.4 deaths per 100 person years)
- methadone maintenance program (MMT) participation was associated with lower mortality
- Enrollment in MMT was also associated with lower rates of non-overdose mortality
- Our data support the need for universal, unrestricted access to low-threshold MMT

Table 1

Baseline characteristics of 2335 persons who inject drugs (PWID), stratified by methadone use status at study enrollment.

Characteristic	Total (%)* (*n* = 2335)	Enrollment in MMT[a]			
		Yes (%) (*n* = 531)	No (%) (*n* = 1795)	Odds Ratio (95% CI)[b]	*p*-value
Sociodemographic factors					
Male gender	1556 (66.6)	332 (62.5)	1219 (67.9)	0.79 (0.64 – 0.96)	0.021
Median age (Q1 – Q3)[c]	37.3 (29.4 – 43.7)	41.8 (36.0 – 46.2)	35.9 (27.7 – 42.4)	1.92 (1.72 – 2.15)[d]	<0.001
Caucasian ethnicity	1430 (61.2)	414 (78.0)	1012 (56.4)	2.74 (2.19 – 3.43)	<0.001
Unstable housing	1640 (70.2)	357 (67.2)	1275 (71.0)	0.82 (0.67 – 1.02)	0.069
Homelessness[e]	524 (22.4)	125 (23.5)	392 (21.8)	1.11 (0.89 – 1.39)	0.391
Sex-trade involvement[e]	551 (23.6)	106 (20.0)	444 (24.7)	0.76 (0.60 – 0.97)	0.025
HIV infection	642 (27.5)	201 (37.9)	439 (24.5)	1.88 (1.53 – 2.31)	<0.001
Substance use-related behaviors					
≥Daily heroin injection[e]	900 (38.5)	136 (25.6)	759 (42.3)	0.47 (0.38 – 0.58)	<0.001
≥Daily cocaine injection[e]	728 (31.2)	100 (18.8)	626 (34.9)	0.43 (0.34 – 0.54)	<0.001
≥Daily crack cocaine smoking[e]	560 (24.0)	169 (31.8)	385 (21.5)	1.71 (1.38 – 2.12)	<0.001
Median years since first injection (IQR)[c]	14.4 (6.2 – 24.2)	21.7 (13.3 – 28.3)	12.1 (4.7 – 22.1)	1.07 (1.06 – 1.08)	<0.001

[a] MMT = methadone maintenance therapy;

[b] CI = Confidence interval;

[c] Q1–Q3 = 25th – 75th percentiles;

[d] per 10 years older;

[e] all behaviors refer to activities in the prior six months;

* 9 participants with missing values for methadone use at baseline.

Table 2

Bivariable and multivariable Cox regression analyses of the time to all-cause mortality among 2335 persons who inject drugs (PWID).

	Unadjusted Hazard Ratio (HR)			Adjusted† Hazard Ratio (AHR)		
Variable	**RH**	**(95% CI)**	***p*-value**	**ARH**	**(95% CI)[a]**	***p*-value**
Enrollment in MMT[b,c]						
(Yes vs. No)	0.84	(0.70 – 0.99)	0.044	0.73	(0.61 – 0.88)	<0.001
Age						
(Per 10 years older)	1.35	(1.23 – 1.49)	<0.001	1.29	(1.11 – 1.49)	<0.001
HIV infection						
(Yes vs. No)	2.84	(2.38 – 3.39)	<0.001	3.03	(2.53 – 3.64)	<0.001
≥Daily heroin injection[c]						
(Yes vs. No)	0.77	(0.62 – 0.96)	0.022	0.99	(0.78 – 1.24)	0.898

† Model was also adjusted for years since first injection at baseline.

[a] CI = confidence interval;

[b] MMT = methadone maintenance therapy;

[c] Behaviours refer to activities in the last six months.