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Risk of drug related mortality during periods of transition in methadone maintenance treatment: a cohort study

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Risk of drug related mortality during periods of transition in methadone maintenance treatment: a cohort study

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Abstract

This study aims to identify periods of elevated risk of drug related mortality during methadone maintenance treatment (MMT) in primary care using a cohort of 3,162 Scottish drug users between January 1993 and February 2004. Deaths occuring during treatment or within 3 days after last methadone prescription expired were considered as cases "on treatment". Fatalities occuring 4 days or more after leaving treatment were cases "off treatment". 64 drug related deaths were identified. The greatest risk of drug related death was in the first 2 weeks of treatment (Adjusted hazard ratio 2.60, 95% CI 1.03 to 6.56). Risk of drug related death was lower after the first 30 days following treatment cessation, relative to the first 30 days off treatment. History of psychiatric admission was associated with increased risk of drug related death in treatment. Increasing numbers of treatment episodes and urine testing were protective. History of psychiatric admission, increasing numbers of urine tests and co-prescriptions of benzodiazepines increased the risk of mortality out of treatment. The risk of drug related mortality in MMT is elevated during periods of treatment transition, specifically treatment intitiation and the first 30 days following treatment drop-out or discharge.

Introduction

Drug misuse is a major public health problem in Scotland and elsewhere.(ISD, 2004) Heroin users are at high risk of premature mortality, with an annual mortality six times higher than that for a general, age matched population, with more than two-thirds of these deaths due to drug overdose.(Gossop, Stewart, Treacy, & Marsden, 2002) Methadone, is the most common form of treatment for heroin misuse in the UK.(McCowan, Kidd, & Fahey, 2009) Methadone maintenance programmes are commonly provided by general practitioners in the UK, with methadone prescribing in primary care increasing in the 1990s.(Morgan, Griffiths, & Hickman, 2006; Strang & Sheridan, 2003) Despite evidence supporting the benefits of methadone maintenance treatment (MMT), methadone itself has been associated with drug-related deaths.(Cairns, Roberts, & Benbow, 1996; Drummer, Opeskin, Syrjanen, & Cordner, 1992; Harding-Pink, 1993; Morgan, et al., 2006) The risk of overdose has been shown to vary over the course of MMT, with several studies reporting an elevated risk of fatal overdose in the initial weeks of MMT.(Buster, van Brussel, & van den Brink, 2002; Caplehorn & Drummer, 1999; Degenhardt, et al., 2009; Perret, Deglon, Kreek, Ho, & La Harpe, 2000; Deborah Zador & Sunjic, 2000) These effects may arise due to inadequate clinical assessment and review of a patients' tolerance prior to initiating methadone, thus resulting in overdose.(Buster, et al., 2002; Caplehorn & Drummer, 1999) Therefore cautious prescribing of methadone during the first two weeks has been advised based on the risk of cumulative toxicity from methadone.(Zador & Sunjic, 2000)

The risk of methadone overdose must be balanced against the risk of newly inducted patients resorting to illicit drug use to compensate for withdrawal symptoms as they wait for the stabilising effects of methadone to take effect. Such patients may voluntarily withdraw from treatment or, in the case of strict methadone delivery programmes that do not tolerate opiate drug use, be expelled from treatment. Studies have shown that patients who leave methadone programmes have increased mortality risks relative to those remaining in treatment.(Caplehorn, Dalton, Haldar, Petrenas, & et al., 1996; Clausen, Anchersen, & Waal, 2008; Davoli, et al., 2007; Fugelstad, Stenbacka, Leifman, Nylander, & Thiblin, 2007; Langendam, van Brussel, Coutinho, & van Ameijden, 2001; Zanis & Woody, 1998) A recent prospective cohort study of Italian opiate users found that the risk of overdose following treatment cessation was more than three times higher in the first 30 days after treatment drop-out or discharge compared to the subsequent 31 days or more after treatment.(Davoli, et al., 2007) However, these effects are not specific to MMT but rather a range of treatments for heroin dependence, including MMT, methadone detoxification, other pharmacological detoxification and psychological interventions.

The aim of this study is to examine risk of drug related mortality during periods of treatment transition, specifically treatment initiation and the first month following MMT cessation, adjusting for patient characteristics and treatment factors, in a primary care setting in a defined geographical population.

Materials and methods

Study design and setting

A retrospective cohort study design was used. The study population consisted of people resident in Tayside, Scotland, who were registered with a general practitioner and were prescribed and dispensed liquid methadone between January 1993 and February 2004. Every person registered with a general practitioner in Tayside is assigned a 10 digit unique identifier, the Community Health Index (CHI) number, which is used in all encounters with the National Health Service (NHS) in the region.

Procedures

Data on age, sex and postcode for each patient who was dispensed at least one liquid methadone prescription between 1/1/1993 and 28/2/2004 were extracted. Patients who were under 16 or over 65 years of age at the time of first prescription were excluded from the analysis. The CHI number was used to link these records to all dispensed prescribing, hospital admissions, psychiatric unit admissions, urine testing and mortality. Standard operating procedures at the Health Informatics Centre, Univeresity of Dundee were followed to ensure anonymisation of the dataset.(Wilson, 2004)

The movement of patients in and out of treatment was tracked using methadone prescriptions. A patient's first appearance in the dataset was recorded as their first treatment episode during the observation period. Each record of a prescription for methadone contained the date, dose, quantity and strength of the prescription. The

coverage is computed as the quantity divided by the daily dose and is expressed in days. The length of a patient's treatment episode was calculated using the coverage of the patient's prescription. If a patient received a new prescription within three days of the end of the previous prescription's coverage, then they were considered to be still in treatment. When a patient did not receive a new methadone prescription within three days after the end of coverage of a prescription, that patient was considered to have ceased treatment. This 'off treatment' period continued until a patient re-entered treatment as indicated by the presence of a new methadone prescription. A 3 day cut-off was applied according to 1999 UK guidelines, which indicate that a patient may lose their tolerance to methadone after 3 days and need to be reassessed for intoxication and withdrawal before MMT is recommenced.(Department of Health (England) & and the devolved administrations, 1999) This information was used to calculate number and duration of treatment episodes for each patient. Overuse of methadone occured when a patient obtained a new prescription before the end of coverage of the previous prescription. In accordance with UK prescribing guidelines, patients were categorised as below, within or above the recommended methadone maintenance range of 60mg to 120 mg daily.(Department of Health (England) & and the devolved administrations, 2007)

The main outcome measure was drug related mortality recorded on the General Registry Office death certificate. Drug related deaths occuring during treatment or within three days after the final days' coverage of the last methadone prescription were considered as cases during treatment. Fatalities occurring from the fourth day after the final days'

coverage of the last methadone prescription were considered as drug related deaths 'off treatment'.

A number of additional variables were defined as potential explanatory or confounding variables for drug related mortality. The Carstairs deprivation score to categorise socioeconomic status on the basis of home postcode was calculated using 2001 census data and re-expressed as categories.(Carstairs & Morris, 1990) The Charlson comorbidity index was calculated from patient's hospital discharge records for co-morbid disease groups using ICD-9 and ICD-10 codes in the hospital admission records and encashed prescribing records for respiratory disease, AIDS, peptic ulcers, cancer, metastatic tumours, diabetes, myocardial infarction, connective tissue disorders and dementia.(Deyo, Cherkin, & Ciol, 1992; Sundararajan, et al., 2004) The Charlson index scores were categorised into three groups: low (0), medium (1 to 2) and high (≥ 3) morbidity. Psychiatric admissions were recorded for both psychiatric and acute hospitals. Prescribing records were also used to identify all patients who had received benzodiazepines. The dates and results of urine tests for opiates were recorded for each patient. Frequent or moderate urine testing is seen to act as a deterrent to illicit opiate use and thereby improves treatment outcomes. Patients with missing data that prevented calculation of all periods of coverage were excluded from the analysis.

Analysis procedures

We report data statistics as number (percentage) of people for categorical variables. Continuous variables that do not follow a normal distribution were tested using the Shapiro-Wilks test for skewness and reported as the median and interquartile range.

Three Cox proportional hazards models with both time dependent and fixed covariates were used to estimate hazard ratios (HR) and 95% confidence intervals (CI) for drug related mortality during periods of treatment transition. The first model focused on drug related mortality overall. The remaining two models represent subgroup analyses of drug related mortality in treatment and off treatment. Patients were defined by their treatment status at the end of the study or at the time of death. Treatment status was defined according to previous studies (Buster, et al., 2002; Davoli, et al., 2007; Degenhardt, et al., 2009) as : 1-2 weeks in treatment; 3-10 weeks in treatment; >10 weeks in treatment; $\leq$ 30 days off treatment; > 30 days off treatment.

Covariates that had a statistically significant univariate p value ($p<0.05$) were included in the multivariate model. Log transformations were applied to covariates with a highly right-skewed distribution to reduce the effects of extreme values: number of times overusing methadone; number of MMT treatment episodes; number of urine tests for opiate use; and number of prescriptions for benzodiazepines. The proportional hazards assumption was assessed using trend tests of the Schoenfeld residuals with those that failed the assumption entered as continuous time dependent covariates.(Bradburn, Clark, Love, & Altman, 2003) Hazard ratios for variables treated as time dependent covariates

vary over time and are reported at the median survival time. LMAX and DFBETA measures were used to test for influential observations and covariates, respectively. Stata version 11 was used for all statistical analyses.

Results

Description of the study population

A cohort of 3,162 people were prescribed and dispensed methadone during the 12 year study – a total of 14,597 person years with a median follow up of 3.6 (interquartile range 1.5 to 7.5) years.

INSERT TABLE 1 HERE

Table 1 describes the study population. Over half the cohort were aged less than 30 years at the time of first prescription and 45% were from the lowest socioeconomic groups (Carstairs categories 6 and 7). One third of patients had a record of psychiatric admission, and a history of co-prescription of benzodiazepines was high. Half the patients had at least one urine test and were found to overuse their methadone on at least one occasion. The methadone dose at last prescription was lower than the recommended adequate maintenance dose of 60-120mg daily for 74% of patients, with only 25% receiving the recommended adequate maintenance dose (see Table 1). The median number of MMT treatment episodes was 4 (interquartile range 1-11), with a median of 31 days (interquartile range 17 to 41.5) per treatment episode and 40.5 (interquartile range 20 to 575) days per off treatment episode.

Drug related mortality and timing of death

During the 12 year study period, 184 people died. Cause of death was available for 145 (79%) of these people from General Registry Office records. The remaining 39 people were identified as dead from the CHI number register, but cause of death could not be ascertained as there was no General Registry Office record. Codes that relate to 'drug related' were recorded as the principal cause of death in 64 (44%) cases.

Of the 64 drug-related deaths, 31 occurred during treatment (eight in the first two weeks after entering or re-entering treatment, 18 died during the 3rd to the 10th week and 5 died more than 10 weeks after entering or re-entering treatment). Thirty-three patients died after treatment drop-out or discharge, 11 died in the first 30 days following treatment cessation.

High risk periods

Table 2 shows the risk of drug related mortality at different time points in and out of methadone treatment, adjusted for significant covariates. The risk of mortality is significantly lower after the first month following treatment drop-out or discharge relative to the first 30 days following treatment cessation (Adjusted HR 0.06, 95% CI 0.02 to 0.14, $p<0.001$). However, the risk of mortality during the first two weeks of treatment is substantially higher than the off treatment risk period of less than one month post treatment with an adjusted HR 2.60 (95% CI 1.03 to 6.56, $p<0.05$). Greater movement in and out of treatment, a history of psychiatric admission and co-prescribing of benzodiazepines remained independently associated with increased risk of drug related

mortality. Older age at time of first prescription was found to be protective of drug related mortality (table 2).

INSERT TABLE 2 HERE

A more detailed look at the risk of drug related mortality during MMT is shown in table 3. The risk of drug related death was markedly elevated in the first two weeks following treatment intitiation. Retention in treatment for 3-10 weeks and greater than 10 weeks was found to be protective against drug related mortality. These effects remained after adjusting for significant covariates. A history of psychiatric admission was found to increase the risk of drug related death in treatment (Adjusted HR 9.51, 95% CI 3.15 to 28.69, $p < 0.001$). Increasing numbers of treatment episodes and urine testing for opiates were found to be protective (table 3).

INSERT TABLE 3 HERE

As displayed in the overall risk model, the risk of mortality during the first 30 days following treatment cessation has an increased risk of mortality relative to the subsequent 31 days or more after leaving treatment (Adusted HR 0.17, 95% CI 0.06 to 0.47, $p < 0.01$). A history of psychiatric admission (Adjusted HR 8.48, 95% CI 3.44 to 20.94, $p < 0.001$) and increasing numbers of urine tests for opiates and co-prescriptions for benzodiazepines increased the risk of mortality out of treatment (table 4).

INSERT TABLE 4 HERE

Discussion

As hypothesised, periods of transition, particularly treatment initiation and the first month following discontinuation, were identified as high risk periods for drug related deaths in and out of treatment. This study also highlights the chronic relapsing nature of drug use. Few patients were retained in treatment for the duration of the observation period, rather patients moved in and out of treatment, experiencing multiple treatment episodes and treatment discontinuation. These findings are consistent with previous studies.(Bell, Burrell, Indig, & Gilmour, 2006; Degenhardt, et al., 2009; Nosyk, et al., 2009)

This study was the first study to consider sub-group analyses, examining the influence of patient and treatment factors on drug related deaths overall, and on deaths in treatment and following treatment cessation. In the overall model, risk of drug related death increased with greater numbers of treatment episodes, a history of psychiatric admission and co-prescribing of benzodiazepines. Greater numbers of treatment episodes indicates greater movement in and out of treatment during the study period which may arise due to a chaotic lifestyle with increased exposure to the known risk periods, the first two weeks in treatment and first month off treatment. The increased hazard of death among those with co-prescriptions for benzodiazepines is consistent with previous research (Man, Best, Gossop, Stillwell, & Strang, 2004) and toxicological reports of drug related deaths.(Zador, et al., 2005).

History of psychiatric admission remained significantly associated with an increased risk of death in treatment. Increasing numbers of urine tests in treatment were protective

against mortality in treatment. The protective effects of urine testing may arise due to greater monitoring of patients in treatment which may equate with greater contact with health professionals. In contrast to the overall model, number of treatment episodes was found to be associated with reduced mortality in treatment. An Australian study reported similar findings, with increased prior treatment episodes associated wtih reduced risk during treatment induction.(Degenhardt, et al., 2009) Degenhardt and colleagues also found that the majority of these induction deaths occured in the first two treatment episodes. Similarly, we found that half of the drug related deaths occurring in the first two weeks of treatment occured in the first three treatment episodes. The protective effects of number of treatments may reflect selection effects, with those at hightest risk dying early.(Degenhardt, et al., 2009) Furthermore, patients experiencing more treatment episodes are likely to have more regular contact with health services which may be protective against drug related mortality in treatment. In addition, a recent Canadian study of MMT found that patients experiencing multiple treatment episodes tended to stay in treatment for progressively longer periods in later episodes.(Nosyk, et al., 2009) We found similar effects in this study, suggesting greater stability over time which may offer protection against mortality in treatment. Similarly, a recent study of the Edinburgh Addiction Cohort found that for each additional year of methadone therapy the hazard of death before long term heroin cessation fell 13%.(Kimber, et al., 2010) It is also important to note that number of treatment episodes was not identified as time dependent in the 'in' treatment model. Failure to account for time may have confounded our results.

In relation to drug related deaths out of treatment, the risk is greatest in the first month following treatment cessation. The risk of death increased among those with a history of psychiatric admission and co-prescribing of benzodiazepines. In addition, those with greater numbers of urine testing off treatment had an increased hazard of mortality off treatment. It is interesting to note that number of treatment episodes, although not significant at a multivariate level of analysis, increased the risk of mortality off treatment. It is possible that the negative effects of multiple treatment and cessation episodes are greatest during off treatment periods. However, this is speculative and would require further investigation.

Strengths and limitations

The strengths of the study include the study size, long duration of follow-up and detailed prescribing, monitoring and management information over time. In addition, NICE guidelines indicate that most randomised controlled trials of methadone therapy in the treatment of drug dependence were done in ouptatient of inpatient settings or specialist treatment centres.(National Institute for Health and Clinical Excellence.Methadone and buprenorphine for the management of opioid dependence, 2007) This study focuses on identifying periods of increased mortality risk among community based patients.

Due to the observational study design, causal interpretations can be only plausibly inferred. The choice of high risk periods (i.e. the first two weeks in treatment, the first thirty days off treatment) were chosen based on published evidence.(Buster, et al., 2002; Davoli, et al., 2007) A different choice of high risk periods may influence the relative

importance of the different risk factors associated with mortality. As mortality was a relatively rare event, this study may have been underpowered to detect potentially significant contributions of some factors. In addition, we could not identify cause of death for 39 cases of the total cohort who died during the study period. Other shortcomings relate to the limited details regarding on and off treatment episodes. In relation to 'on' treatment episodes we do not have infomation regarding supervised consumption or other therapeutic experiences such as counselling. In addition, we have limited information regarding patient circumstances during 'off' treatment episodes. Time after discontinuation of treatment may be spent in prison, or a patient may relapse or fully abstain from illicit drug use. Such differences are likely to confound the ability of our study to accurately stratify risk of mortality off treatment. However, we do know that even if a patient left Tayside during an 'off treatment' episode they did not register with another GP outside Tayside. Although we adjusted for several confounders, other confounders such as addiction severity, route of admission, imprisonment and living situation, which we have not accounted for may bias the results. Finally, the generalisability of these results may be limited as the movement of patients in and out of treatment was more frequent in this cohort compared to other longitudinal studies.(Bell, et al., 2006; Degenhardt, et al., 2009; Nosyk, et al., 2009) A median of 4 treatment episodes was recorded in our study with an interquartile range of 1-11 treatment episodes. A recent Canadian study of MMT over an 11 year follow-up recorded a median of two treatment episodes with an IQR 1-3.(Nosyk, et al., 2009) However, this discrepancy may be an artefact of differential definitions of when an 'off' treatment episode begins. Our

study considered treatment cessation to occur after 3 days compared to a 7 day cut-off in the Canadian study.

Implications

Notwithstanding these limitations, the current findings have important implications for practice and policy. Firstly, given the increased risk of mortality during periods of treatment transition, efforts should be made to encourage patient retention in MMT programmes as part of a drug overdose prevention strategy. The importance of retaining patients in treatment is also highlighted as greater frequency of movement in and out of treatment was found to be related to drug related mortality. A post-treatment follow-up should also be considered following treatment cessation, particularly in the first month following treatment drop-out or discharge. Similarly, a stringent clinical assessment and review of a patients' tolerance prior to starting MMT is important to avoid drug-overdose during treatment induction espcially for those with fewer previous treatment episodes. Previous studies have also highlighted that opiate users with help-seeking behaviours are more likely to attempt suicide.(Ghodse, Sheehan, Taylor, & Edwards, 1985) Therefore, clinicians should also seek to identify those patients with suicidal ideation at the time of treatment commencement. Finally, the delivery of MMT in primary care may not be appropriate for all patients, particularly those patients with psychiatric co-morbidities. Patients with a history of psychiatric admission were identified as having an elevated risk of mortality both on and off treatment, however further evidence is required to stratify the influence of various psychiatric conditions on mortality during MMT in primary care.

Conclusions

This community based study shows an elevated risk of drug related mortality during periods of treatment transition, particularly the first two weeks of treatment initiation and the first 30 days following treatment drop-out or discharge. The quality of care could be improved by ensuring greater monitoring of methadone patients when starting or restarting a patient on MMT. In addition, a post-treatment follow-up should also be considered following treatment cessation, particularly in the first month following treatment drop-out or discharge.

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Table 1. Description of the study population, according to whether patients survived or died

Characteristics	Surviving patients (n=3,098)	Drug-related death 'in treatment' (n=31)	Drug-related death 'off treatment' (n=33)	Total (n=3,162)
Male sex	2003 (64.7)	18 (58.1)	27 (81.8)	2048 (64.8)
Age:				
16-19	297 (9.6)	1 (3.2)	2 (6.1)	300 (9.5)
20-29	1413 (45.6)	21 (67.7)	22 (66.7)	1456 (46.1)
30-39	795 (25.7)	7 (22.6)	7 (21.2)	809 (25.6)
40-65	593 (19.1)	2 (6.5)	2 (6.1)	597 (18.9)
Social class (Carstairs)[a]:				
1	56 (1.9)	0	0	56 (1.8)
2	243 (8.0)	0	0	243 (7.9)
3	501 (16.6)	4 (12.9)	4 (12.1)	509 (16.5)
4	332 (11.0)	4 (12.9)	2 (6.1)	338 (10.9)
5	537 (17.7)	5 (16.1)	8 (24.2)	550 (17.8)
6	782 (25.8)	9 (29.0)	13 (39.4)	804 (26.0)
7	576 (19.0)	9 (29.0)	6 (18.2)	591 (19.1)
Comorbidity (Charlson Index):				
0	2752 (88.8)	22 (71.0)	26 (78.8)	2800 (88.6)
1-2	221 (7.1)	3 (9.7)	5 (15.2)	229 (7.2)
≥ 3	125 (4.0)	6 (19.4)	2 (6.1)	133 (4.2)
Psychiatric admission	988 (31.9)	27 (87.1)	25 (75.8)	1040 (32.9)
Urine tests for opiates	1542 (49.8)	17 (54.8)	14 (42.4)	1573 (49.8)
Co-prescribing of	1974 (63.7)	30 (96.8)	30 (90.9)	2034 (64.3)

Benzodiazepines				
Characteristics	**Surviving patients (n=3,098)**	**Drug-related death 'in treatment' (n=31)**	**Drug-related death 'off treatment' (n=33)**	**Total (n=3,162)**
Overusing methadone	1521 (49.1)	25 (80.7)	22 (66.7)	1568 (49.6)
Last methadone dose:				
< 60 mg	2298 (74.2)	26 (83.9)	25 (75.8)	2349 (74.3)
60 – 120 mg	781 (25.2)	5 (16.1)	8 (24.2)	794 (25.1)
≥ 120 mg	19 (0.6)	0	0	19 (0.6)
Median number MMT episodes	3 (1-11)	7 (4-13)	5 (1-7)	4 (1-11)
Median days In treatment	31 (17-41)	43 (31-59)	38.5 (29.5-70)	31 (17-41.5)
Median days Off treatment	43.5 (20-588)	24 (17-25)	20 (14-54)	40.5 (20-575)

* Data are presented as frequency (percentage) or median (interquartile range)

[a] The number of patients does not add up the total because of some missing data

Table 2. Risk of drug related mortality across different risk periods 'in' and 'off' treatment

Characteristics	Unadjusted hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)
Last treatment episode		
<30 days off methadone (reference)	1.0	1.0
>30 days off methadone	0.32 (0 .15 to 0.65)**	0.06 (0.02 to 0.14)***
1-2 weeks on methadone	2.27 (0.91 to 5.64)	2.60 (1.03 to 6.56)*
>3 weeks on methadone	1.85 (0 .91 to 3.80)	1.97 (0.95 to 4.09)
Male sex	1.19 (0 .70 to 2.04)	NA
Age (per year)	0.96 (0.93 to 0.99)*	0.96 (0.93 to 0.99)**
Social class (Carstairs):		
1-4 (reference)	1.0	NS†
5-7	1.86 (1.03 to 3.37)*	NS†
Comorbidity (Charlson Index):		
0 (reference)	1.0	NS†
1-2	1.90 (0.90 to 4.01)	NS†
≥ 3	2.61 (1.23 to 5.52)*	NS†
Number of times overusing methadone†	1.46 (1.14 to 1.87)**	NS†
Last methadone dose:		
< 60 mg (reference)	1.0	NA
≥ 60 mg	0.75 (0.41 to 1.37)	NA
Number of MMT episodes†	1.67 (1.27 to 2.20)***	1.83 (1.34 to 2.50)***
Psychiatric admission (ever)	6.93 (3.70 to 13.00)***	7.04 (3.55 to 13.97)***
Number of urine tests for opiates†	1.38 (1.06 to 1.79)*	NS†
Number of co-prescriptions for Benzodiazepines	1.34 (1.16 to 1.54)***	1.39 (1.16 to 1.68)***

*p<0.05; **p<0.01; ***P<0.001; † time dependent variable; NA covariates that were non-significant (p>0.05) at the univariate level of analysis were not included in the multivariate model; NS† Social Class, co-morbidity, number of times overusing methadone and number of urine tests for opiates were included in the original multivariate analysis but they did not remain independently significant. Therefore the model was retested removing these variables to improve the power of the model by reducing the number of variables given the small number of events (64).

Table 3. Risk of drug related mortality across different risk periods 'in' treatment

Characteristics	Unadjusted hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)
Last on treatment episode		
1-2 weeks on methadone(reference)	1.0	1.0
3-10 weeks on methadone	0.43 (0.19 to 0.99)*	0.40 (0.17 to 0.95)*
>10 weeks on methadone	0.26 (0.08 to 0.80)*	0.10 (0.03 to 0.35)***
Male sex	0.68 (0.33 to 1.38)	NA
Age (per year)	0.99 (0.94 to 1.04)	NA
Social class (Carstairs):		
1-4 (reference)	1.0	NA
5-7	0.96 (0.43 to 2.16)	NA
Comorbidity (Charlson Index):		
0 (reference)	1.0	NS†
1-2	1.45 (0.43 to 4.84)	NS†
≥ 3	3.02 (1.22 to 7.52)*	NS†
Number of times overusing methadone	0.46 (0.29 to 0.72)**	NS†
Last methadone dose:		
< 60 mg (reference)	1.0	NA
≥ 60 mg	0.42 (0.16 to 1.10)	NA
Number of MMT episodes	0.14 (0.09 to 0.24) ***	0.08 (0.04 to 0.16)***
Psychiatric admission (ever)	6.05 (2.10 to 17.41)**	9.51 (3.15 to 28.69)***
Number of urine tests for opiates	0.37 (0.24 to 0.58)***	0.57 (0.35 to 0.91)*
Number of co-prescriptions for Benzodiazepines	1.15 (0.91 to 1.44)	NA

*p<0.05; **p<0.01; ***P<0.001; NA covariates that were non-significant (p>0.05) at the univariate level of analysis were not included in the multivariate model; NS† Comorbidity and number of times overusing methadone were included in the original multivariate analysis but did not remain independently significant. Therefore the model was retested removing these two variables to improve the power of the model by reducing the number of variables given the small number of events (31).

Table 4. Risk of drug related mortality across different risk periods 'off' treatment

Characteristics	Unadjusted hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)
Last off treatment episode		
<30 days off methadone (reference)	1	1.0
>30 days off methadone	0.41 (0.20 to 0.84)*	0.17 (0.06 to 0.47)**
Male sex	2.30 (0.95 to 5.57)	NA
Age (per year)	0.96 (0.92 to 1.00)	NA
Social class (Carstairs):		
1-4 (reference)	1	
5-7	2.63 (1.09 to 6.38)*	NS†
Comorbidity (Charlson Index):		
0 (reference)	1	NA
1-2	2.30 (0.88 to 6.00)	NA
≥ 3	1.40 (0.33 to 5.92)	NA
Number of times overusing methadone	1.15 (0.86 to 1.53)	NA
Last methadone dose:		
< 60 mg (reference)	1	NA
≥ 60 mg	0.98 (0.44 to 2.18)	NA
Number of MMT episodes†	1.37 (1.06 to 1.79)*	1.27 (0.95 to 1.70)
Psychiatric admission (ever)	5.87 (2.65 to 13.01)***	8.48 (3.44 to 20.94)***
Number of urine tests for opiates†	1.86 (1.19 to 2.93)**	1.72 (1.01 to 2.93)*
Number of co-prescriptions for Benzodiazepines	1.29 (1.07 to 1.56)**	1.31 (1.02 to 1.66)*

*p<0.05; **p<0.01; ***P<0.001; † time dependent variable; NA covariates that were non-significant (p>0.05) at the univariate level of analysis were not included in the multivariate model; NS† Social class was included in the original multivariate analysis but did not remain significant. Therefore the model was retested removing social class to improve the power of the model by reducing the number of variables given the small number of events (33).