# The impact of opiate substitution treatment on mortality in the UK: a natural experiment using the Clinical Practice Research Datalink

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Conflicts of interest

John Marsden acknowledges research grants from the Department of Health, NIHR and the NIHR BRC for Mental Health at King's Health Partners, and part-time employment as Senior Academic Advisor for the Alcohol, Drugs and Tobacco Division, Health Improvement Directorate, Public Health England. He declares investigator-led, educational grant funding from Indivior PLC (administered by Action-on-Addiction) for a study of adjunctive,

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Tim Millar has received research funding from the UK National Treatment Agency for Substance Misuse, Public Health England and the Home Office. He has been a member of the organising committee for conferences supported by unrestricted educational grants from Reckitt Benckiser, Lundbeck, Martindale Pharma, and Britannia Pharmaceuticals Ltd, for which he received no personal remuneration. He is a member of the UK Advisory Council on the Misuse of Drugs.

John Strang is a clinician and researcher and has worked extensively with agencies in the addiction treatment fields and addiction-related charities and with government departments and has contributed to clinical guidelines on treatment types and provision. JS's employer (King's College London) has received, connected to his work, project grant support and/or honoraria and/or consultancy payments from Department of Health, NTA (National Treatment Agency), PHE (Public Health England), Home Office, NICE (National Institute for Health and Clinical Excellence), and EMCDDA (European Monitoring Centre for Drugs and Drug Addiction) as well as research grants from (last 3 years) NIHR (National Institute on Health Research), MRC (Medical Research Council) and Pilgrim Trust. He has also worked with WHO (World Health Organization), UNODC (United Nations Office on Drugs and Crime), EMCDDA, FDA (US Food and Drug Administration) and NIDA (US National Institute on Drug Abuse) and also other international government agencies. JS's employer (King's College London) has also received, connected to his work, research grant support and/or payment of honoraria, consultancy payments and expenses from pharmaceutical companies (including, past 3 years, Martindale, Indivior, MundiPharma, Braeburn/Camurus)

and trial medication supply from iGen and Braeburn. JS's employer (King's College London) has registered intellectual property on an innovative buccal naloxone with which JS is involved, and JS has been named in a patent registration by a Pharma company as inventor of a potential concentrated naloxone nasal spray. For updated information see http://www.kcl.ac.uk/ioppn/depts/addictions/people/hod.aspx

Matt Hickman has received unrelated unrestricted honoraria from Gilead, Abbvie, Jansen and Merck Serono. MH is a member of the PHR Research Funding Board.
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**Scientific summary**

*Background*

Opioid drug misuse is a major concern in the UK affecting up to 350,000 individuals. Opiate substitute treatment (OST) is a common and effective treatment with methadone and buprenorphine being the two types of medication most often prescribed. Studies have shown increased risks of mortality during the first few weeks at the start of treatment and the period immediately following cessation of treatment. Only one study has examined how the risk profile may vary between methadone and buprenorphine. But being based in Australia it is unclear whether a similar pattern of risks applies to the UK.

Clinical guidelines recommend a low initial dose with dose increasing over the first weeks until a maintenance dose is achieved. Similarly, treatment should cease after a period of tapering doses ending with a low dose. The guidelines also advise caution in the use of benzodiazepines with OST patients due to the possible drug interaction and the association of multi-drug exposure with mortality.

Observational studies are prone to residual confounding related to causal factors omitted from the analyses or poorly measured. Methods such as Self-Controlled Case Series (SCCS) methods are robust to such confounders, if their data does not vary with time, and may be helpful in identifying causal effects.

*Objectives*

This project aimed to address five main objectives associated with the five work packages.

1. To investigate the trends in the delivery of OST and how this relates to the clinical guidelines.
2. To explore factors affecting the risk of mortality with particular reference to OST type and OST treatment period.

3. To explore the effects of co-prescription on the risk of mortality amongst OST patients. Investigations considered not only benzodiazepines but also z-drugs and gabapentinoids.
4. To explore the effects of dose regimens during induction and during detoxification on mortality risks. Investigations considered regimens in terms of starting/ending doses and the change in dose over the first/last 28 days of treatment.
5. To investigate how SCCS methods might be modified in the context of OST and the implications of their results.

*Methods*

This study utilised data collected prospectively within UK primary care and administered by the Clinical Practice Research Datalink (CPRD). Four main types of information were extracted

(a) Patient socio-demographic information

This included basic information such as age and gender but also details about a patient's history of custodial sentences, alcohol problems and overdose.

(b) Medications prescribed

This information was used to identify OST patients but also co-prescribed medications, such as benzodiazepines, which may affect mortality risk. Information of dose was also important.

(c) Practice characteristics

This included information of the practice location within the UK, practice size in terms of the number of GPs and the number of OST patients.

(d) Date and cause of death

Unlike date of death, cause of death was not routinely recorded within CPRD. However, their data was linked to other UK databases allowing cause of death to be extracted from an Office of National Statistics database. Unfortunately, at the time of this study, only about 50% of patients had been linked limiting patients eligible for drug related poisonings (DRP) analyses. All patients were eligible for the analysis of all cause mortality (ACM).

The identification of OST patients involved primarily those receiving at least 20mg of methadone or 4mg of buprenorphine at some time. Considerable efforts were made to exclude patients receiving these medications for pain relief. Patients receiving at least 480mg of dihydrocodeine were also included where there was other evidence that these prescriptions were part of OST. In total, 13,005 patients were identified between the study dates of 1st January 1998 to 31st July 2014. In mortality analyses, up to 12,118 patients were utilised reflecting those with ages between 15 to 64 years.

Poisson regression was the main method used to analyse mortality data. However, a variety of other methods and weighting of the data, most notably inverse probability weighting (IPW), were employed to obtain more robust results or used as sensitivity analyses.

*Results*

The main results are listed below by objective. For objective 1, the main results on the trends in prescribing practice were:

- Patients receiving OST may have reached a peak in 2008 with current numbers about 20% lower than at that time.
- The use of methadone within OST has been declining while buprenorphine use has been increasing up to about 2006. After this date, there was less evidence of any relative change in the use of these medications.
- Co-prescription of benzodiazepines has been declining throughout the study period while the co-prescription of gabapentinoids has been increasing. Co-prescription of z-drugs has not changed substantially during the study period.
- Average doses for both methadone and buprenorphine reached their maxima around 2008. Similarly, the proportion of episodes reaching an optimal maintenance dose was improving up to 2008 but declining (methadone) or no change (buprenorphine) after this date.

- On and off treatment duration were generally increasing throughout the study period. Buprenorphine had both shorter on and off treatment durations.

For objective 2, the results on OST type and mortality can be summarised as:

- Mortality risks were lowest during treatment after the first four weeks. Elevated risks were observed in the first four weeks of treatment and in the first 4 weeks following cessation of treatment.
- Differences between methadone and buprenorphine treatment were most pronounced in the first four weeks of treatment but also during the remainder of time on treatment although the evidence was much weaker for DRP. Here methadone had higher risks than buprenorphine. Potentially inconsistent results were obtained for the first four weeks following cessation with ACM showing a protective effect for buprenorphine while DRP showed no difference although the best estimate of the difference also showed a protective effect.
- Differences between methadone and buprenorphine for the period after four weeks since treatment had ceased were attributed to residual confounding despite robust methods such as IPW supporting this difference.
- The effect of OST type was observed to vary with age and comorbidity such that buprenorphine had stronger protective associations amongst older or more comorbid patients.

For objective 3, the main results on co-prescription and mortality were:

- Co-prescription of benzodiazepines increased the risk of mortality for DRP.
- Co-prescription of z-drugs increased the risk of mortality for ACM and DRP.
- Co-prescription of gabapentinoids increased the risk of mortality for ACM, DRP and non-drug related deaths.
- Concurrent exposure of benzodiazepines and z-drugs increased treatment duration but did not reduce overall ACM or DRP mortality risk.

For objective 4, the main results on the associations of initiation and cessation regimens with mortality were:

- Higher starting and ending doses were associated with increased mortality for ACM.
- Increasing the observation period from 28 days to 56 days did not change these effect sizes but increased the weight of statistical evidence due to the increased number of deaths.
- There was no consistent evidence that change in dose in the first or last 28 days affected the risk of mortality.
- There was no evidence that these effects varied with OST type.
- Too few deaths were eligible for DRP analyses to draw any reliable conclusions.
- There was some evidence that adherence to guidelines with starting and ending doses was improving after 2007 compared to before this date.

For objective 5, the main results from the modified SCCS methods provide some support for the interaction between OST type and period. The Farrington method for ACM showed similar protective effects for buprenorphine during the first four weeks of both the start of treatment and after the end of treatment. However, there was no evidence of a similar beneficial effect after the first four weeks of treatment. The Kuhnert method for ACM provided weak evidence of an interaction but with the wide CIs, it was difficult to interpret. Both SCCS methods for DRP provided no evidence of an interaction but with wide CIs it may suggest these analyses were underpowered.

*Conclusions*

Our findings provided a conflicting picture on overall mortality rates related to methadone and buprenorphine treatments. While analyses of mortality data suggested a beneficial effect for buprenorphine and suggests advantages in prescribing buprenorphine especially during induction, simulations based upon drug related poisoning mortality rates under a scenario of induction with buprenorphine with methadone thereafter were more equivocal on the net effect.

All cause mortality rates increased after cessation of treatment. This may be the result of poor retention during detoxification in the final stages of treatment or poor coping mechanisms following the planned cessation of treatment. Both are likely to benefit from greater patient support.

Our data suggested that the co-prescription of benzodiazepines and z-drugs had a detrimental association with mortality. While recent guidelines suggest caution in prescribing OST to patients with benzodiazepine dependence, this study suggests the warnings should be extended to prescribing benzodiazepines and z-drugs to patients undergoing OST.

There was evidence that adherence to clinical guidelines on dosing, in particular low starting and ending doses, may help to reduce mortality. Results for change in dose based upon a 28-day window were equivocal but this may have reflected too short a period in which to assess changes in dose.

Our study was limited by the availability of data on the addiction severity, the quality of OST (for instance the use of supervised consumption) and the extent of psychosocial support. It is possible that such factors may have confounded our results.

Further work is needed to replicate our findings. In particular, such studies could clarify the role of gabapentinoids on mortality risk and whether the older or more comorbid patients benefit from buprenorphine treatment compared to methadone treatment. Larger population-based data sets or more specialised data sets on addiction may help to identify the role on initiation and cessation dosing regimens on drug related mortality which our study was under-powered to evaluate.