The impact of opiate substitution treatment on mortality risk in drug addicts: a natural experiment study

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Scientific summary

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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 an increased risk of mortality during the first few weeks at the start of treatment and in the period immediately following cessation of treatment. Only one study has examined how the risk profile may vary between methadone and buprenorphine, but as that study was based in Australia it is unclear whether or not a similar pattern of risk applies in the UK.

Clinical guidelines recommend a low initial dose and then increasing the dose over the first few 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 when using benzodiazepines with OST patients because of the possible drug interaction and the association of multidrug exposure with mortality.

Observational studies are prone to residual confounding related to causal factors that are omitted from the analyses or are poorly measured. Methods such as self-controlled case series (SCCS) are robust to such confounders, if their data do 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 these relate to the clinical guidelines.
2. To explore factors affecting the risk of mortality, with particular reference to OST type and OST period.
3. To explore the effects of co-prescription on the risk of mortality among 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 risk. 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:

1. Patient sociodemographic 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.
2. Medications prescribed – this information was used to identify OST patients but also co-prescribed medications, such as benzodiazepines, that may affect mortality risk. Information on dose was also important.
3. Practice characteristics – this included information about the practice's location in the UK, and the practice size in terms of the number of general practitioners and the number of OST patients.

4. Date and cause of death – unlike date of death, cause of death was not routinely recorded within CPRD. However, data were linked to other UK databases, allowing cause of death to be extracted from an Office for National Statistics database. Unfortunately, at the time of this study, only about 50% of patients had been linked, limiting the patients eligible for drug-related poisoning (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 20 mg of methadone or 4 mg of buprenorphine at some time. Considerable efforts were made to exclude patients receiving these medications for pain relief. Patients receiving at least 480 mg of dihydrocodeine were also included when there was other evidence that these prescriptions were part of OST. In total, 13,005 patients were identified between the study dates of 1 January 1998 and 31 July 2014. In mortality analyses, up to 12,118 patients were utilised, reflecting those with ages between 15 and 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, were employed to obtain more robust results or were 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 as follows.

- 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, whereas buprenorphine use increased up to about 2006. After this date, there was less evidence of any relative change in the use of these medications.
- The co-prescription of benzodiazepines declined during the study period while the co-prescription of gabapentinoids increased. The co-prescription of z-drugs did not change substantially during the study period.
- The average doses of both methadone and buprenorphine reached their maxima around 2008. Similarly, the proportion of episodes reaching an optimal maintenance dose improved up to 2008 but declined (methadone) or did not change (buprenorphine) after this date.
- On- and off-treatment duration generally increased during the study period. Buprenorphine had a shorter duration for both on and off treatment.

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

- Mortality risk was lowest during treatment after the first 4 weeks. Elevated risks were observed in the first 4 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 4 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 4 weeks following cessation, with ACM showing a protective effect for buprenorphine and DRP showing no difference, although the best estimate of the difference also showed a protective effect.
- The differences between methadone and buprenorphine for the 4 weeks after treatment had ceased were attributed to residual confounding, despite robust methods such as inverse probability weighting supporting this difference.
- The effect of OST type was observed to vary with age and comorbidity such that buprenorphine had stronger protective associations among older or more comorbid patients.

For objective 3, the main results on co-prescription and mortality were as follows.

- 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 of the associations of initiation and cessation regimens with mortality were as follows.

- Higher starting and ending doses were associated with increased ACM.
- Increasing the observation period from 28 days to 56 days did not change these effect sizes but increased the weight of statistical evidence as a result of 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 allow any reliable conclusions to be drawn.
- There was some evidence that adherence to guidelines with starting and ending doses was improving after 2007 compared with 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 4 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 4 weeks of treatment. The Kuhnert method for ACM provided weak evidence of an interaction but, with the wide confidence intervals, it was difficult to interpret. Both SCCS methods for DRP provided no evidence of an interaction but the wide confidence intervals may suggest that these analyses were underpowered.

Conclusions

Our findings provided a conflicting picture of overall mortality rates related to methadone and buprenorphine treatments. Although analyses of mortality data suggested a beneficial effect for buprenorphine and suggested advantages to prescribing buprenorphine, especially during induction, simulations based on DRP 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 the 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. Although recent guidelines suggest caution in prescribing OST to patients with benzodiazepine dependence, this study suggests that 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. The results for change in dose based on 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 (e.g. 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 older or more comorbid patients benefit from buprenorphine treatment more than from methadone treatment. Larger population-based data sets or more specialised data sets on addiction may help to identify the role of initiation and cessation dosing regimens on drug-related mortality, which our study was underpowered to evaluate.

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