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# Association between benzodiazepine co-prescription and mortality in people on opioid replacement therapy: a population-based cohort study



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**TITLE PAGE**

**Title: Association between benzodiazepine co-prescription and mortality in people on opioid replacement therapy: a population-based cohort study**

**Running title:** Benzodiazepine co-prescription with ORT

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**ABSTRACT**

**Objective**: To investigate the association between Opioid Replacement Therapy and benzodiazepine co-prescription and all-cause mortality compared to the prescription of Opioid Replacement Therapy alone.

**Design**: Population based cohort study

**Setting**: Scotland, UK.

**Participants**: Participants were people prescribed Opioid Replacement Therapy between January 2010 and end of December 2020 aged 18 years or above.

**Main outcome measures**: all-cause mortality, drug related deaths and non-drug related deaths. **Secondary outcome**: Opioid Replacement Therapy continuous treatment duration.

**Analysis:** Cox regression with time-varying covariates.

**Results:** During follow up 5776 of 46899 participants died: 1398 while on co-prescription and 4378 while on Opioid Replacement Therapy only. The mortality per 100 person years was 3.11 during co-prescription and 2.34 on Opioid Replacement Therapy only. The adjusted hazard ratio for all-cause mortality was 1.17 (1.10 to 1.24). The adjusted hazard ratio for drug related death was 1.14 (95% CI 1.04 to 1.24) and the hazard for death not classified as drug-related was 1.19 (95% CI 1.09 to 1.30).

**Conclusion:** Co-prescription of benzodiazepines in opioid replacement therapy increased risk of all cause mortality. However, it was also associated with longer retention in treatment. In treatment planning, risk from benzodiazepine co-prescription needs to be balanced against the risk from illicit benzodiazepines and unplanned treatment discontinuation.

Strengths and limitations of this study

- A strength of this analysis is the large and inclusive population approach that included the whole Opioid Replacement Therapy treatment population in Scotland over 10 years.
- Compared to the existing literature this study is one of the larger studies conducted.
- A weakness of this study is that the analysis has not considered dose of Opioid Replacement Therapy, or benzodiazepine, which will be variable within individuals over time.

**Keywords:** benzodiazepines, opioid replacement therapy, mortality, treatment retention, survival analysis, Scotland

## INTRODUCTION

We have an ongoing challenge in the UK and abroad on how to address the risks associated with illicit drug use. In recent years there have been remarkably high numbers of deaths reported in Scotland, with increasing numbers recorded in England and Wales and Northern Ireland. The opioid crisis of north America is also well documented. (1) However a strong feature associated with increasing deaths in the UK is that of concurrent use of benzodiazepines alongside opiate drugs. This does not occur in isolation and may be compounded by use of alcohol, cocaine and gabapentinoids.

Nowhere is the issue more apparent than in Scotland where the rise of the use of non-prescription benzodiazepines is clear. In 2008 benzodiazepines were implicated in 26% (n=149) of drug related deaths and were mainly drugs licensed for prescription such as diazepam. By 2018 benzodiazepines and benzodiazepine-type drugs were implicated in 67% (792) of DRD, predominately substances not licensed for prescription in the UK such as etizolam (a thenodiazepine). Since then the trend has continued with a range of novel benzodiazepines emerging.

People who use non-prescription benzodiazepines, of unknown constituents and potency, can consume 'megadoses' of benzodiazepines many times in excess of safe therapeutic doses, often with alcohol and other drugs, which combine to increase the risk of harm and death. (2, 3) People presenting to addiction services for initial assessment frequently report illicit benzodiazepine use in the month prior to assessment, an average of 2561 (29%) per year in a five-year period. (4) The prevalence of illicit benzodiazepine use is known to be higher among people with other substance use disorders, especially problematic opiate and/or alcohol dependence. (5) A systematic review identified a high prevalence (typically >40%) among people on Opiate Replacement Therapy (ORT). (6) In Scotland, the Drug Deaths Taskforce, as a pragmatic approach, developed interim Guidance for clinicians to support the management of problematic 'street' benzodiazepine use alongside opiate use. (7) Whilst some addiction services are now exploring maintenance prescribing to reduce the risks associated with illicit benzodiazepine use among ORT patients, there is considerable and understandable reluctance given the potential risk and lack of evidence of risk and benefit. The available clinical guidance only supports maintenance prescribing in exceptional cases. (7, 8)

Evidence of patient safety and other outcomes is developing internationally with recent studies added to the evidence base. A recent systematic review of these studies found that of six identified studies that looked at all-cause mortality, five recorded an increased risk (9-12) However, of the seven studies that looked at retention in treatment, there were favourable findings in three studies with better retention for those co-prescribed a benzodiazepine with ORT, no difference in two studies and variable findings depending on time for one study. (10, 11, 13-17) One study that analysed the impact of prescribed versus street benzodiazepine use among ORT patients receiving methadone found prescribed benzodiazepine improved treatment retention whereas non prescribed benzodiazepine (i.e. street drug use) was predictive of treatment drop out. (15) Thus there are opposing risks and benefits associated with benzodiazepine prescribing for those receiving ORT. Much of the existing evidence is based on large epidemiological studies of administrative prescribing and outcome datasets. However, the follow up time for many of these studies is limited and it is important to understand the longer-term implications of co-prescription.

This study sought to further understand patterns of, and outcomes from benzodiazepine prescribing among ORT patients over a 10-year period to inform safe and effective clinical practice.

## METHODS

This was an observational, retrospective cohort study using routinely collected administrative data in Scotland. Participants were followed from their first ORT prescription after 1st January 2010 until the time they were known to have died, or until 31st December 2020 as shown in Figure 1.

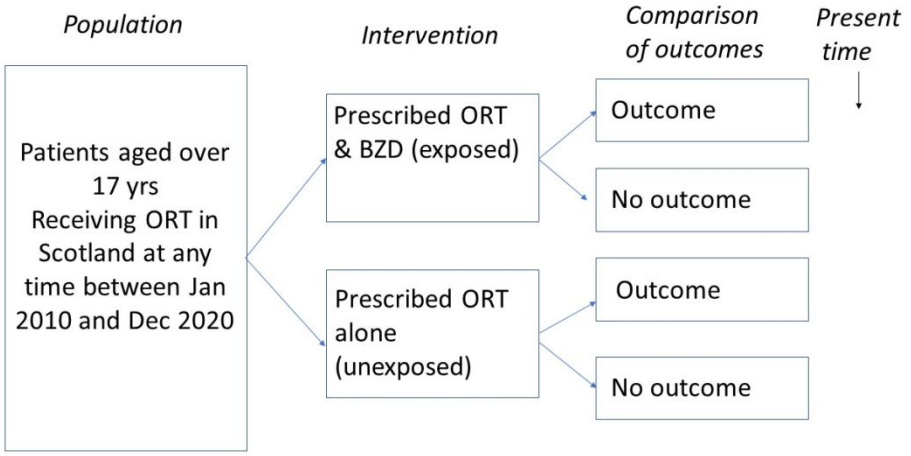


**Figure 1 Cohort study design diagram**

### *Cohort identification*

The study population were people dispensed ORT where prescribing was coded using British National Formulary codes for "drugs used in substance dependence". (18) The inclusion criteria were all individuals prescribed ORT between 1st January 2010 and 31st December 2020 and who were aged 18 years or above.

This study used data from Public Health Scotland which included the Prescribing Information System (PIS) and the National Records of Scotland (NRS) Vital Events. (19, 20) The PIS contains information on all medicines and their costs that are prescribed and dispensed in the community in Scotland. The information is supplied by Practitioner & Counter Fraud Services Division who are responsible for the processing and pricing of all prescriptions dispensed in Scotland. GPs write the majority of these prescriptions, with the remainder written by other authorised prescribers such as nurses, psychiatrists, pharmacists and dentists. Also included in the dataset are prescriptions written in hospitals that are dispensed in the community. Prescriptions dispensed within hospitals are not included. Linkage of data from diverse sources was conducted by electronic Data Research and Innovation Service (eDRIS) which is part of Public Health Scotland. Data sets were joined by deterministic linkage based on each patients' unique Community Health Index number. (21) Data were held in the national Safe Haven and all analyses were undertaken in the Safe Haven by approved researchers. (22)

***'On treatment' definition***

Individuals were defined as being 'on ORT treatment' if the time was less than 101 days from the dispensed date of their previous ORT prescription. This period was defined empirically from the distribution of observed dispense date intervals for ORT prescription.

***ORT and benzodiazepines included***

ORT drugs included methadone and buprenorphine. Benzodiazepines included alprazolam, chlordiazepoxide, clobazam, clonazepam, diazepam, flurazepam, loprazolam, lorazepam, lormetazepam, nitrazepam, oxazepam, temazepam

***Time varying exposure definition***

The exposure was defined as an individual being within 40 days of the dispensing of their most recent prescription of a benzodiazepine. The time of 40 days was defined empirically as the time window that captured the majority of inter-prescription time periods for repeat benzodiazepine prescriptions in this cohort.

***Continuous treatment episode definition***

A treatment episode is defined here as a continuous time period where an individual was receiving ORT prescriptions at intervals of 100 days or less.

**ANALYSIS**

Descriptive statistics were used to characterise the demographics (age, gender, urban/rural classification, area-level socioeconomic deprivation) of exposed and unexposed groups.

The primary analysis was a time-to-event analysis by Cox Regression. The Cox proportional hazards model allowed us to compare the instantaneous hazard for mortality during time periods where there was co-prescription of ORT and a benzodiazepine compared to the hazard where ORT was prescribed alone. The exposure was included as a time varying covariate. All models presented are adjusted for age at first ORT prescription dispensed, age at first dispense squared, and age at first

dispense cubed, sex, Scottish Index of Multiple Deprivation and Scottish urban rural classification, ever prescription of z-drugs and ever prescription of opioid analgesics.

Three outcomes were examined in separate regression models: all-cause mortality, drug-related deaths, and non-drug related deaths. Effect sizes are presented as hazard ratios and their 95% confidence intervals.

In secondary analyses we examined a different definition of the exposure: any prescription of benzodiazepine during the study period. That is, we examined whether any prescription of a benzodiazepine during the study period was associated with increased mortality. This was done by including benzodiazepine prescription as a time-invariant covariate. Then we tested whether the observed effects differed by the type of ORT prescription. That is, we examined the effects of methadone and buprenorphine separately.

In further analyses, we examined the average continuous treatment episode duration for episodes where ORT was prescribed alone compared to episodes of co-prescription with a benzodiazepine. Differences in duration were tested by regression analysis adjusted for age and sex.

All analyses were conducted in Stata version 17. (23)

***Patient and Public Involvement***

The research questions were informed by consulting people with personal experience of substance use and/or addiction care and/or non-fatal overdose and/or affected by another person's drug-related death. Members of two voluntary sector recovery communities were consulted in 2019: Aberdeen in Recovery and Forth Valley Recovery Community. Nineteen people were consulted and received a £10 supermarket voucher stipend for their time and contributions. All those consulted supported the study concept and research questions. All supported analysis of pseudonymised patient data on the condition that individuals could not be identified by academic researchers or in project outputs. All appreciated the plan to develop a public-facing, accessible, plain language summary of results for dissemination to people who use drugs.

The research team and the project Advisory Group both include at least two people with lived experience of problematic substance use and addiction service use.

***Ethical approval***

Access for data to conduct this study was approved (ref 2021-0154) by the NHS Scotland Public Benefit and Privacy Panel for Health and Social Care which is a governance structure of NHS Scotland. (24)

**RESULTS**

***Description of sample***

The total number of prescriptions dispensed for the cohort was approximately 17 million of which 5 494 857 prescriptions were for ORT or BZD. The cohort was made up of 48588 individuals and was approximately two thirds male. The cohort was disproportionately from areas characterised by high levels of deprivation relative to the general population reflecting the fact those in low Social Index of Multiple Deprivation (SIMD) deciles (high deprivation) are more likely to be receiving ORT and/or

BZD as shown in Table 1. There was also higher ORT prescribing in urban areas which may be confounded by socioeconomic deprivation. Of the full cohort, 55.9% received a benzodiazepine prescription at some time between January 2010 and December 2020. Socio-demographics are presented in table 1 according to BZD exposure (irrespective of length or number of prescriptions). Slightly more women had ever received a benzodiazepine compared to men (62.7% of females, 53.9% of males on BZD) which was statistically significant (Chi square=447, df=1 p<0.001).

**Table 1 Sociodemographic characteristics of cohort**

| | | Any BZD (exposed) | No BZD (unexposed) | Full sample |
|---|---|---|---|---|
| | N= | 27184 | 21404 | 48588 |
| Sex | Male | 17155 (63.11%) | 15451 (72.19%) | 32606 (67.11%) |
| | Female | 10029 (36.89%) | 5953 (27.81%) | 15982 (32.89%) |
| SIMD decile | 1 (Highest deprivation) | 8811 (32.41%) | 7055 (32.96%) | 15866 (32.65%) |
| | 2 | 5477 (20.15%) | 4367 (20.40%) | 9844 (20.26%) |
| | 3 | 3925 (14.44%) | 2933 (13.70%) | 6858 (14.11%) |
| | 4 | 2757 (10.14%) | 2091 (9.77%) | 4848 (9.98%) |
| | 5 | 1880 (6.92%) | 1417 (6.62%) | 3297 (6.79%) |
| | 6 | 1388 (5.11%) | 1026 (4.79%) | 2414 (4.97%) |
| | 7 | 1005 (3.70%) | 723 (3.38%) | 1728 (3.56%) |
| | 8 | 723 (2.66%) | 598 (2.79%) | 1321 (2.72%) |
| | 9 | 525 (1.93%) | 400 (1.87%) | 925 (1.90%) |
| | 10 (Lowest deprivation) | 367 (1.35%) | 357 (1.67%) | 724 (1.49%) |
| | Missing | 326 (1.20%) | 437 (2.04%) | 763 (1.57%) |
| Urban-rural classification 2016 | Large urban areas | 13359 (49.14%) | 10249 (47.88%) | 23608 (48.59%) |
| | Other urban areas | 9516 (35.01%) | 7746 (36.19%) | 17262 (35.53%) |
| | Accessible small towns | 1508 (5.55%) | 1183 (5.53 %) | 2691 (5.54%) |
| | Remote small towns | 824 (3.03%) | 587 (2.74 %) | 1411 (2.90%) |
| | Accessible rural areas | 1164 (4.28%) | 869 (4.06%) | 2033 (4.18%) |
| | Remote rural areas | 476 (1.75%) | 325 (1.52%) | 801 (1.65%) |
| | Missing | 337 (1.24%) | 445 (2.08 %) | 782 (1.61%) |

***All-cause mortality, drug related deaths and non-drug related deaths***

During follow up 5776 participants died: 1398 while on co-prescription of a benzodiazepine and ORT and 4378 while on ORT only. The total time under observation for all participants in the study was 232282 years. The total time under observation while on benzodiazepine prescription and ORT was 45046 years (mean per participant 2.21 years, median per participant 1.09 years) and the total time on ORT only 187236 years (mean per participant 4.09, median per participant 3.36 years). The mortality per 100 person years was 3.11 during co-prescription and 2.34 on ORT only.

This section outlines the results of three Cox regressions examining the effect of co-prescription of benzodiazepines on the outcomes: all-cause mortality, drug related deaths and deaths not classified as drug related.

The total number of participants included in the Cox regression analysis was 46899. There were 5776 deaths from any cause during the time period. Of these 2938 were drug-related deaths and 2838 were not classified as drug-related deaths.

Table 2 shows the hazard ratio and 95% confidence interval for the effect of benzodiazepine co-prescription versus ORT only on the three mortality outcomes.

**Table 2: Effect of co-prescription of a benzodiazepine on outcomes in people receiving opioid replacement therapy**

| Outcome | Hazard Ratio[a] | *p* | 95% CI | |
|---|---|---|---|---|
| All-cause mortality | 1.17 | <0.001 | 1.10 | 1.24 |
| Drug related death | 1.14 | 0.003 | 1.04 | 1.24 |
| Not drug related death | 1.19 | <0.001 | 1.09 | 1.30 |

[a] adjusted for age at first ORT prescription dispensed, age at first dispense squared, and age at first dispense cubed, sex, Scottish Index of Multiple Deprivation, Scottish urban-rural classification, ever prescription of z-drugs, and ever prescription of opioid analgesics

After adjustment, the effect of exposure (co-prescription of benzodiazepines in the last 40 days) increased the hazard for all-cause mortality relative to ORT alone, by 17% (HR 1.17 95% CI 1.10 to 1.24) it increased the hazard for drug-related death by 14% (HR 1.14 95% CI 1.04 to 1.24) and it increased the hazard for death not classified as drug-related by 19% (HR 1.19 95% CI 1.09 to 1.30).

***All-Cause Mortality by ORT drug***

All-cause mortality (ACM) was analysed by type of ORT (methadone and buprenorphine). Being 'on ORT treatment' was defined as being within 100 days of the last methadone prescription. Then we repeated the analysis with the definition that on treatment was being within 100 days of the last buprenorphine prescription.

**Table 3: Comparison of results with methadone versus buprenorphine opioid prescription**

| ORT definition | Haz. Ratio | *p* | 95% CI | |
|---|---|---|---|---|
| Methadone | 1.41 | <0.001 | 1.32 | 1.50 |
| Buprenorphine | 1.16 | 0.189 | 0.93 | 1.44 |

Table 3 shows that methadone with a co-prescribed benzodiazepine was associated with an increase hazard of ACM compared to methadone alone whereas buprenorphine plus co-prescribed benzodiazepines was not associated with an increased hazard for ACM.

***Retention in Treatment***

Table 4 shows the descriptive statistics for treatment episodes broken down by whether the treatment episodes was for ORT only or ORT and a benzodiazepine.

**Table 4: Treatment episode length for ORT episodes with and without a benzodiazepine co-prescription**

| | All ORT episodes | ORT with any benzodiazepine co-prescription | ORT with no benzodiazepine prescriptions |
|---|---|---|---|
| N episodes | 121435 | 37022 | 84413 |
| Median (days) | 375 | 678 | 312 |
| IQR (days) | 153-1005 | 222-1645 | 131-749 |
| Mean (days) | 766.27 | 1110.29 | 615.38 |
| Std. Dev. (days) | 920.06 | 1118.86 | 770.75 |

A comparison of episode duration between ORT episodes with no benzodiazepine co-prescription and episodes of ORT with benzodiazepine co-prescription by linear regression with adjustment for age and sex found the coefficient for a benzodiazepine episode was 540.58 days (95% CI 528.56 to 552.61days). This indicates that treatment episodes are around 541 days longer (i.e. retention in treatment better) when there is benzodiazepine co-prescription than episodes with ORT alone after adjustment for age and sex of the person receiving treatment.

***Model Refinement and Sensitivity Analysis***

We considered the possibility that there may be some dilution of the model due to inclusion of non-ORT opiates e.g. for pain or the use chlordiazepoxide for alcohol detoxification. Frequencies of prescriptions for these drugs are:

- Chlordiazepoxide: 0.2% of all prescriptions, and 0.841% of all benzodiazepine prescriptions, 6.5% of patients were ever prescribed this.
- Temgesic: 0.03% of prescriptions, and 0.30% analgesic opioid prescriptions, 0.56% of patients were ever prescribed this.
- Buprenorphine patches: 0.10% of all prescriptions, and 0.92% of all analgesic opioid prescriptions, were for buprenorphine patches. 0.6% of patients were ever prescribed buprenorphine patches.

We concluded that Temgesic and buprenorphine patches were present in very small percentage of opioid prescriptions and patients and are therefore unlikely to affect the model. Chlordiazepoxide represented less than 1% of BZD prescriptions, however it was present in 6.5% of patients.

Further sensitivity analyses were conducted to test the effects of varying the time periods used to define continuous treatment episodes for ORT (100 days in main analysis but varied to 365 days here) and continuous treatment episodes for benzodiazepine (40 days for main and analysis but varied to 60 and 28 days here). The results shown in table 5 are from cox regression analyses and are adjusted for the same covariates as the main analyses. The analysis found the association between benzodiazepine co-prescription and increased hazard for mortality was robust to variations in the

time frame used to define continuous treatment episodes. When either the time frame for benzodiazepine or ORT continuous treatment was extended then the hazard ratio between groups was larger. When both were extended at the same time this was not the case.

**Table 5 Sensitivity analyses**

| All cause mortality | | | | | |
|---|---|---|---|---|---|
| ORT duration | BZD duration | Hazard ratio | p | 95% Conf. Interval | |
| 100 | 60 | 1.41 | <0.001 | 1.33 | 1.49 |
| 100 | 28 | 1.17 | <0.001 | 1.10 | 1.25 |
| 365 | 60 | 1.17 | <0.001 | 1.10 | 1.24 |
| 365 | 28 | 1.58 | <0.001 | 1.49 | 1.69 |
| Drug related deaths | | | | | |
| 100 | 60 | 1.39 | <0.001 | 1.27 | 1.51 |
| 100 | 28 | 1.17 | <0.001 | 1.08 | 1.26 |
| 365 | 60 | 1.13 | <0.001 | 1.04 | 1.22 |
| 365 | 28 | 1.55 | <0.001 | 1.42 | 1.69 |
| Non-drug-related deaths | | | | | |
| 100 | 60 | 1.42 | <0.001 | 1.30 | 1.54 |
| 100 | 28 | 1.17 | <0.001 | 1.08 | 1.26 |
| 365 | 60 | 1.20 | <0.001 | 1.11 | 1.30 |
| 365 | 28 | 1.60 | <0.001 | 1.46 | 1.74 |

## DISCUSSION

### *Summary of main findings*

Findings indicated an increased risk of ACM, drug related death and non-drug related death in our cohort when comparing those co-prescribed a benzodiazepine compared to ORT with no prescribed benzodiazepine exposure. However, when analysed by ORT drug, methadone with a co-prescribed benzodiazepine increased hazard of ACM whereas buprenorphine plus a co-prescribed benzodiazepine did not. Retention in treatment was increased when co-prescribed a benzodiazepine alongside ORT compared to ORT alone.

The ACM hazard ratio for combined ORT (methadone and buprenorphine) concurs with the international literature although the risk in this study appears to be lower (17% increase of ACM, 14% for DRD and 19% for non-drug death) than in other studies of equivalent size and methodological approach (range 70-90% for ACM). (9, 11, 25) There was a higher level of non-drug related death than drug related death within ACM which is indicative of other risks being posed by benzodiazepine use. This group of drugs, indeed sedatives in general, have long been known to increase risk of accidents and falls so this finding could reflect this general risk associated with this drug group.

This study was able to compare ACM by ORT drug. Analysis found buprenorphine did not increase risk of ACM. One study in the literature looked specifically at buprenorphine ACM and whilst there was an increased risk (HR 1.9) (11) this is lower than for the studies that combined ORT drugs or

looked at methadone alone. Taken together these findings suggest that buprenorphine poses less risk in combination with a benzodiazepine. This may be because buprenorphine causes less respiratory depression than methadone (26). There may, however, be bias in treatment allocation to methadone or buprenorphine as people who are prescribed methadone could have particular characteristics which pre-dispose them to increased risk of harm. Methadone is associated with more sedation than buprenorphine (26) which is welcomed by some compared to the 'clear headedness' that buprenorphine provides (27). In addition, it is possible that the smaller number of participants in buprenorphine-only sample, reduced the statistical power to detect effects of co-prescription in this group.

Retention in treatment was significantly longer for those with a benzodiazepine co-prescription than those on ORT alone. This finding concurs with the literature (28). Evidence strongly implies that treatment is protective of overdose (29), therefore keeping people in contact with treatment services, and avoiding unplanned discharge is generally considered protective. The sensitivity analysis found extending the period of ORT (365 day compared to 100 days) and benzodiazepine prescribing (60 days compared to 40 days) reduced the relative effect of benzodiazepine prescription on ACM. This could be because increasing the time window for both benzodiazepine and ORT prescription means we include more people who have disengaged from treatment within the analysis meaning the baseline risk increases and therefore there is less of an effect of co-prescription. This interpretation requires further research to confirm or refute.

Overall the effect size was lower than other studies in the literature. To explore this we undertook further sensitivity analysis. Firstly we considered if there had been a dilution effect e.g. due to opiate drugs for non ORT purposes, specifically Temgesic$^{R}$ and buprenorphine patches, prescribed for pain. In addition we considered the potential inclusion of chlordiazepoxide for alcohol detoxification. However these formed a very small percentage (<1%) of all prescriptions and cases so were not considered to have affected the findings. Therefore we can conclude that whilst there is a raised ACM overall, Scotland appears to have a lower HR ACM compared to other countries. This may well be a factor related to the characteristics of the Scottish treatment population. For example we have high levels of mental and physical co-morbidity in the Scottish drug using population (30) . Brands et al also noted the different clinical profile in people who use BZD highlighting there are more women and more psychiatric conditions. In other words, this is evidence that benzodiazepine and opiate users have more co-morbid risk. (31) This was not specifically tested in our analysis but would be an important plausible explanation given the known high levels of co-occurring mental health problems (30).

There is also a high level of other drugs (as well as benzodiazepines) implicated in DRD in Scotland, which has increased over time, specifically gabapentinoids, cocaine and alcohol are all relatively frequently implicated. This is indicative of a higher risk pattern of drug use in this population. It may be that the many in the ORT group were also using street benzodiazepines so were already exposed to increased risk.

***Methodological Considerations***

A strength of this analysis is the large and inclusive population approach that included the whole ORT treatment population over 10 years. Compared to the existing literature this study is one of the

larger studies conducted. The analysis has not considered dose of ORT, or benzodiazepine, which will be variable within individuals over time.

There are some important caveats to this analysis that must be taken into consideration in any further reporting or referencing of this work. This is a treatment population and does not compare ACM for those prescribed a benzodiazepine and ORT with those not receiving a prescribed benzodiazepine and a prescribed ORT i.e. those still using street drugs. The risk of ACM for people who are using non-medical opioids, from a recent meta-analysis is a standardised mortality ratio of 10 (95% CI, 7.6-13.2) (32). This does not account for benzodiazepine prescribing.

***Clinical Implications***

Clinicians need to weigh up the risks to patients of being exposed to the street market of illicit drugs and the impact of a controlled prescribed alternative, recognising that street benzodiazepines will still be available. Overall improved retention in treatment is an important clinical consideration. Keeping people in treatment longer allows time to address some of the mental health factors that may contribute to street benzodiazepine use.

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STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

| | Item No | Recommendation | Page No |
|---|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | Title & Abstract page 1 &2 |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | Title & Abstract page 1 &2 |
| **Introduction** | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | 3-4 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | 3-4 |
| **Methods** | | | |
| Study design | 4 | Present key elements of study design early in the paper | 4-5 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 5-6 |
| Participants | 6 | (*a*) Give the eligibility criteria, and the sources and methods of selection of participants | 5 |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 6 |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | *6* |
| Bias | 9 | Describe any efforts to address potential sources of bias | 6 |
| Study size | 10 | Explain how the study size was arrived at | 6 |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 6 |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | 6 |
| | | (*b*) Describe any methods used to examine subgroups and interactions | 6 |
| | | (*c*) Explain how missing data were addressed | NA |
| | | (*d*) If applicable, describe analytical methods taking account of sampling strategy | NA |
| | | (*e*) Describe any sensitivity analyses | 7 |
| **Results** | | | |
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | 7 |
| | | (b) Give reasons for non-participation at each stage | |
| | | (c) Consider use of a flow diagram | |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | 7, Table 1 |
| | | (b) Indicate number of participants with missing data for each variable of interest | Table 1 |

| | | | |
|---|---|---|---|
| Outcome data | 15* | Report numbers of outcome events or summary measures | 8 |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | 9 |
| | | (*b*) Report category boundaries when continuous variables were categorized | NA |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | 9 |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | 12 |
| **Discussion** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | 13 |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | 13 |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | 13 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | 13 |
| **Other information** | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | Title page |

*Give information separately for exposed and unexposed groups.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

# Association between benzodiazepine co-prescription and mortality in people on opioid replacement therapy: a population-based cohort study



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**TITLE PAGE**

**Title: Association between benzodiazepine co-prescription and mortality in people on opioid replacement therapy: a population-based cohort study**

**Running title:** Benzodiazepine co-prescription with ORT

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**Study registration details:** This study was preregistered at clinicaltrials.gov with record number NCT04622995.

## ABSTRACT

**Objective**: To investigate the association between Opioid Replacement Therapy (ORT) and benzodiazepine co-prescription and all-cause mortality compared to the prescription of ORT alone.

**Design**: Population based cohort study

**Setting**: Scotland, UK.

**Participants**: Participants were people prescribed ORT between January 2010 and end of December 2020 aged 18 years or above.

**Main outcome measures**: all-cause mortality, drug related deaths and non-drug related deaths.
**Secondary outcome**: ORT continuous treatment duration.

**Analysis:** Cox regression with time-varying covariates.

**Results:** During follow up 5776 of 46899 participants died: 1398 while on co-prescription and 4378 while on ORT only. The mortality per 100 person years was 3.11 during co-prescription and 2.34 on ORT only. The adjusted hazard ratio for all-cause mortality was 1.17 (1.10 to 1.24). The adjusted hazard ratio for drug related death was 1.14 (95% CI 1.04 to 1.24) and the hazard for death not classified as drug-related was 1.19 (95% CI 1.09 to 1.30).

**Conclusion:** Co-prescription of benzodiazepines in opioid replacement therapy was associated with an increased risk of all-cause mortality, although with a small effect size than the international literature. Co-prescribing was also associated with longer retention in treatment. Risk from benzodiazepine co-prescription needs to be balanced against the risk from illicit benzodiazepines and unplanned treatment discontinuation. A randomised controlled trial is urgently needed to provide clear clinical direction.


Strengths and limitations of this study

- A strength of this analysis is the population-based analysis that included the whole Opioid Replacement Therapy treatment population in Scotland.
- A strength of this analysis is that follow up took place over 10 years
- A weakness of this study is that the analysis has not considered dose of Opioid Replacement Therapy, or benzodiazepine, which will be variable within individuals over time.
- A weakness of the study is that there is potential residual unmeasured confounding that means that the relationship between benzodiazepine co-prescription and mortality cannot be assumed to be causal.

**Keywords:** benzodiazepines, opioid replacement therapy, mortality, treatment retention, survival analysis, Scotland

## INTRODUCTION

We have an ongoing challenge in the UK and abroad on how to address the risks associated with illicit drug use. Opioid replacement treatment (ORT) is a well evidenced treatment which has provided a safe and effective treatment to reduce the risks of illicit opiate use. (1) Despite this, in recent years there have been remarkably high numbers of deaths reported in Scotland, with increasing numbers recorded in England and Wales and Northern Ireland. The opioid crisis of north America is also well documented. (2) A strong feature associated with increasing deaths in the UK is that of concurrent use of benzodiazepines alongside opiate drugs. (3) This does not occur in isolation and may be compounded by use of alcohol, cocaine and gabapentinoids. (3, 4)

Nowhere is the issue more apparent than in Scotland where the rise of the use of non-prescription benzodiazepines is clear. In 2008 benzodiazepines were implicated in 26% (n=149) of drug related deaths and were mainly drugs licensed for prescription such as diazepam. By 2018 benzodiazepines and benzodiazepine-type drugs were implicated in 67% (792) of drug-related deaths (DRD), reducing slightly to 57% in 2022 (3). Benzodiazepines identified are predominately substances not licensed for prescription in the UK such as etizolam (a thenodiazepine) but there is an ongoing trend of novel benzodiazepines emerging (5)

People who use non-prescription benzodiazepines, of unknown constituents and potency, can consume 'megadoses' of benzodiazepines many times in excess of safe therapeutic doses, often with alcohol and other drugs, which combine to increase the risk of harm and death. (5, 6) People presenting to addiction services for initial assessment frequently report illicit benzodiazepine use in the month prior to assessment, an average of 2561 (29%) per year in a five-year period. (7) The prevalence of illicit benzodiazepine use is known to be higher among people with other substance use disorders, especially problematic opiate and/or alcohol dependence. (8, 9) A systematic review identified a high prevalence (typically >40%) of illicit benzodiazepine use among people on Opiate Replacement Therapy (ORT). (10) In Scotland, the Drug Deaths Taskforce, as a pragmatic approach, developed interim Guidance for clinicians to support the management of problematic 'street' benzodiazepine use alongside opiate use. (11) Whilst some addiction services are now exploring maintenance prescribing to reduce the risks associated with illicit benzodiazepine use among opioid replacement therapy (ORT) patients, there is considerable and understandable reluctance given the potential risk and lack of evidence of risk and benefit. The available clinical guidance only supports maintenance prescribing in exceptional cases. (11, 12)

Evidence of patient safety and other outcomes is developing internationally with recent studies added to the evidence base. A recent systematic review of these studies found that of six identified studies that looked at all-cause mortality, four recorded co-prescription to be associated with an increased risk. (13, 14, 16, 17) However, of the seven studies that looked at retention in treatment, there were favourable findings in three studies with those co-prescribed a benzodiazepine with ORT remaining in treatment longer (14, 15, 17). No difference in two studies and variable findings depending on time for one study. (18-20) One study that analysed the impact of prescribed versus street benzodiazepine use among ORT patients receiving methadone found prescribed benzodiazepine improved treatment retention whereas non prescribed benzodiazepine (i.e. street

drug use) was predictive of treatment drop out. (21) Thus there are opposing risks and benefits associated with benzodiazepine prescribing for those receiving ORT. Much of the existing evidence is based on large epidemiological studies of administrative prescribing and outcome datasets. However, the follow up time for many of these studies is limited and it is important to understand the longer-term implications of co-prescription. Given the particular problems highlighted in Scotland, this study sought to further understand patterns of, and outcomes from benzodiazepine prescribing among ORT patients over a 10-year period to inform safe and effective clinical practice.

## METHODS

This was an observational, retrospective cohort study using routinely collected administrative data in Scotland. Participants were followed from their first ORT prescription after 1st January 2010 until the time they were known to have died, or until 31st December 2020.

Figure 1 Time to event analysis- lines denote time in study for each participant.

**Figure 1 Time to event analysis**

### *Cohort identification*

The study population were people dispensed ORT where prescribing was coded using British National Formulary codes for "drugs used in substance dependence". (22) The inclusion criteria were all individuals prescribed ORT between 1st January 2010 and 31st December 2020 and who were aged 18 years or above.

This study used data from Public Health Scotland which included the Prescribing Information System (PIS) and the National Records of Scotland (NRS) Vital Events. (23) The PIS contains information on all medicines and their costs that are prescribed and dispensed in the community in Scotland. The information is supplied by Practitioner & Counter Fraud Services Division who are responsible for the processing and pricing of all prescriptions dispensed in Scotland. GPs write the majority of these prescriptions, with the remainder written by other authorised prescribers such as nurses, psychiatrists, pharmacists and dentists. Also included in the dataset are prescriptions written in hospitals that are dispensed in the community. Prescriptions dispensed within hospitals are not included. Linkage of data from diverse sources was conducted by electronic Data Research and Innovation Service (eDRIS) which is part of Public Health Scotland. Data sets were joined by deterministic linkage based on each patients' unique Community Health Index number. (24) Data were held in the national Safe Haven and all analyses were undertaken in the Safe Haven by approved researchers. (25)

***'On treatment' definition***

To determine the 'on treatment' definition we examined the time interval between repeat prescription of ORT in the dataset. Prescription intervals of 90 days were found to be the most common. Individuals were defined as being 'on ORT treatment' if the time was less than 101 days from the dispensed date of their previous ORT prescription as this allows some leeway for holidays and illness around the most common prescription interval of 90 days. Thus, the time period used in the 'on treatment' definition was defined empirically from the distribution of observed dispense date intervals for ORT prescription. Individuals were included in the analyses while they were 'on treatment'.

***ORT and benzodiazepines included***

ORT drugs included methadone and buprenorphine. Benzodiazepines included alprazolam, chlordiazepoxide, clobazam, clonazepam, diazepam, flurazepam, loprazolam, lorazepam, lormetazepam, nitrazepam, oxazepam, and temazepam.

***Time varying exposure definition***

The exposure was defined as an individual being within 40 days of the dispensing of their most recent prescription of a benzodiazepine. The time of 40 days was defined empirically as the time window that captured the majority of inter-prescription time periods for repeat benzodiazepine prescriptions in this cohort.

***Continuous treatment episode definition***

A treatment episode is defined here as a continuous time period where an individual was receiving ORT prescriptions at intervals of 100 days or less.

***Demographic variables***

Socioeconomic deprivation was assessed by the Scottish Index of Multiple Deprivation (SIMD) based on post code of residence. Scotland is divided into around 7000 small areas which are ranked in terms of deprivation across the domains of: income, employment, education, health access to services, crime, and housing to create the SIMD (26). Area of residence was also categorised using the Scottish Government's Urban Rural Classification which is based on population and accessibility (27). Age in years and sex were also available for the cohort.

**ANALYSIS**

Descriptive statistics were used to characterise the demographics (age, gender, urban/rural classification, area-level socioeconomic deprivation) of exposed and unexposed groups.

The primary analysis was a time-to-event analysis by Cox Regression. Figure 1 is an illustration of data for the time to event analysis. The Cox proportional hazards model allowed us to compare the instantaneous hazard for mortality during time periods where there was co-prescription of ORT and a benzodiazepine compared to the hazard where ORT was prescribed alone. The exposure was included as a time varying covariate. All models presented are adjusted for age at first ORT prescription dispensed, age at first dispense squared, and age at first dispense cubed, sex, Scottish Index of Multiple Deprivation and Scottish urban rural classification, ever prescription of z-drugs and ever prescription of opioid analgesics.

Three outcomes were examined in separate regression models: all-cause mortality, drug-related deaths, and non-drug related deaths. Effect sizes are presented as hazard ratios and their 95% confidence intervals.

In secondary analyses we examined a different definition of the exposure: any prescription of benzodiazepine during the study period. That is, we examined whether any prescription of a benzodiazepine during the study period was associated with increased mortality. This was done by including benzodiazepine prescription as a time-invariant covariate. Then we tested whether the observed effects differed by the type of ORT prescription. That is, we examined the effects of methadone and buprenorphine separately.

In further analyses, we examined the average continuous treatment episode duration for episodes where ORT was prescribed alone compared to episodes of co-prescription with a benzodiazepine. Differences in duration were tested by regression analysis adjusted for age and sex.

As the definition of 'on treatment' for ORT was determined from prescription intervals observed in this dataset we performed sensitivity analyses varying the time window for defining being on ORT treatment and for the exposure i.e. benzodiazepine co-prescription. If the effect of co-prescription on mortality outcomes was only observed under one particular definition of 'on treatment ' or exposure then this would indicate that the association may be a chance observation. However, if the effect is robust under a number of definitions, then this is support for the association.

All analyses were conducted in Stata version 17. (28)

***Patient and Public Involvement***

The research questions were informed by consulting people with personal experience of substance use and/or addiction care and/or non-fatal overdose and/or affected by another person's drug-related death. Members of two voluntary sector recovery communities were consulted in 2019: Aberdeen in Recovery and Forth Valley Recovery Community. Nineteen people were consulted and received a £10 supermarket voucher stipend for their time and contributions. All those consulted supported the study concept and research questions. All supported analysis of pseudonymised patient data on the condition that individuals could not be identified by academic researchers or in project outputs. All appreciated the plan to develop a public-facing, accessible, plain language summary of results for dissemination to people who use drugs.

The research team and the project Advisory Group both include at least two people with lived experience of problematic substance use and addiction service use.

***Ethical approval***

Access for data to conduct this study was approved (ref 2021-0154) by the NHS Scotland Public Benefit and Privacy Panel for Health and Social Care which is a governance structure of NHS Scotland. (29)

## RESULTS

### *Description of sample*

The total number of prescriptions dispensed for the cohort was approximately 17 million of which 5 494 857 prescriptions were for ORT or BZD. The cohort was made up of 48588 individuals and was approximately two thirds male. The cohort was disproportionately from areas characterised by high levels of deprivation relative to the general population reflecting the fact those in low Social Index of Multiple Deprivation (SIMD) deciles (high deprivation) are more likely to be receiving ORT and/or BZD as shown in Table 1. There was also higher ORT prescribing in urban areas.. Of the full cohort, 55.9% received a benzodiazepine prescription at some time between January 2010 and December 2020. Socio-demographics are presented in table 1 according to whether the participant had BZD exposure at any time during the study period (irrespective of length or number of prescriptions). Slightly more women had ever received a benzodiazepine compared to men (62.8% of females, 52.6% of males on BZD) which was statistically significant (Chi square=447, df=1 p<0.001). There was no association between exposure and either social deprivation or urbanicity.

**Table 1 Sociodemographic characteristics of cohort**

| | | Any BZD (exposed) | No BZD (unexposed) | Full sample | p |
|---|---|---|---|---|---|
| | N= | 27184 | 21404 | 48588 | |
| Sex | Male | 17155 (63.11%) | 15451 (72.19%) | 32606 (67.11%) | <0.001 |
| | Female | 10029 (36.89%) | 5953 (27.81%) | 15982 (32.89%) | |
| SIMD decile | 1 (Highest deprivation) | 8811 (32.41%) | 7055 (32.96%) | 15866 (32.65%) | 0.704 |
| | 2 | 5477 (20.15%) | 4367 (20.40%) | 9844 (20.26%) | |
| | 3 | 3925 (14.44%) | 2933 (13.70%) | 6858 (14.11%) | |
| | 4 | 2757 (10.14%) | 2091 (9.77%) | 4848 (9.98%) | |
| | 5 | 1880 (6.92%) | 1417 (6.62%) | 3297 (6.79%) | |
| | 6 | 1388 (5.11%) | 1026 (4.79%) | 2414 (4.97%) | |
| | 7 | 1005 (3.70%) | 723 (3.38%) | 1728 (3.56%) | |
| | 8 | 723 (2.66%) | 598 (2.79%) | 1321 (2.72%) | |
| | 9 | 525 (1.93%) | 400 (1.87%) | 925 (1.90%) | |
| | 10 (Lowest deprivation) | 367 (1.35%) | 357 (1.67%) | 724 (1.49%) | |
| | Missing | 326 (1.20%) | 437 (2.04%) | 763 (1.57%) | |
| Urban-rural classification 2016 | Large urban areas | 13359 (49.14%) | 10249 (47.88%) | 23608 (48.59%) | 0.689 |
| | Other urban areas | 9516 (35.01%) | 7746 (36.19%) | 17262 (35.53%) | |
| | Accessible small towns | 1508 (5.55%) | 1183 (5.53 %) | 2691 (5.54%) | |
| | Remote small towns | 824 (3.03%) | 587 (2.74 %) | 1411 (2.90%) | |
| | Accessible rural areas | 1164 (4.28%) | 869 (4.06%) | 2033 (4.18%) | |
| | Remote rural areas | 476 (1.75%) | 325 (1.52%) | 801 (1.65%) | |
| | Missing | 337 (1.24%) | 445 (2.08 %) | 782 (1.61%) | |

***All-cause mortality, drug related deaths and non-drug related deaths***

During follow up 5776 participants died: 1398 while on co-prescription of a benzodiazepine and ORT and 4378 while on ORT only. The total time spent in the study for all participants was 232282 years. The total time in the study while on benzodiazepine prescription and ORT was 45046 years (mean per participant 2.21 years, median per participant 1.09 years) and the total time on ORT only 187236 years (mean per participant 4.09, median per participant 3.36 years). The mortality per 100 person years was 3.11 during co-prescription and 2.34 on ORT only.

This section outlines the results of three Cox regressions examining the effect of co-prescription of benzodiazepines on the outcomes: all-cause mortality, drug related deaths and deaths not classified as drug related.

The total number of participants included in the Cox regression analysis was 46899. There were 5776 deaths from any cause during the time period. Of these 2938 were drug-related deaths and 2838 were not classified as drug-related deaths.

Table 2 shows the hazard ratio and 95% confidence interval for the effect of benzodiazepine co-prescription versus ORT only on the three mortality outcomes.

**Table 2: Effect of co-prescription of a benzodiazepine on outcomes in people receiving opioid replacement therapy**

| Outcome | Hazard Ratio[a] | *p* | 95% CI | |
|---|---|---|---|---|
| All-cause mortality | 1.17 | <0.001 | 1.10 | 1.24 |
| Drug related death | 1.14 | 0.003 | 1.04 | 1.24 |
| Not drug related death | 1.19 | <0.001 | 1.09 | 1.30 |

[a] adjusted for age at first ORT prescription dispensed, age at first dispense squared, and age at first dispense cubed, sex, Scottish Index of Multiple Deprivation, Scottish urban-rural classification, ever prescription of z-drugs, and ever prescription of opioid analgesics

After adjustment, the effect of exposure (co-prescription of benzodiazepines in the last 40 days) increased the hazard for all-cause mortality relative to ORT alone, by 17% (HR 1.17 95% CI 1.10 to 1.24) it increased the hazard for drug-related death by 14% (HR 1.14 95% CI 1.04 to 1.24) and it increased the hazard for death not classified as drug-related by 19% (HR 1.19 95% CI 1.09 to 1.30).

***All-Cause Mortality by ORT drug***

All-cause mortality (ACM) was analysed by type of ORT (methadone and buprenorphine). Being 'on ORT treatment' was defined as being within 100 days of the last methadone prescription. Then we repeated the analysis with the definition that on treatment was being within 100 days of the last buprenorphine prescription.

**Table 3: Comparison of results with methadone versus buprenorphine opioid prescription**

| ORT definition | Haz. Ratio | *p* | 95% CI | |
|---|---|---|---|---|
| Methadone | 1.41 | <0.001 | 1.32 | 1.50 |
| Buprenorphine | 1.16 | 0.189 | 0.93 | 1.44 |

Table 3 shows that methadone with a co-prescribed benzodiazepine was associated with an increase hazard of ACM compared to methadone alone whereas buprenorphine plus co-prescribed benzodiazepines was not associated with an increased hazard for ACM.

***Retention in Treatment***

Table 4 shows the descriptive statistics for treatment episodes broken down by whether the treatment episodes was for ORT only or ORT and a benzodiazepine.

**Table 4: Treatment episode length for ORT episodes with and without a benzodiazepine co-prescription**

| | All ORT episodes | ORT with any benzodiazepine co-prescription | ORT with no benzodiazepine prescriptions |
|---|---|---|---|
| N episodes | 121435 | 37022 | 84413 |
| Median (days) | 375 | 678 | 312 |
| IQR (days) | 153-1005 | 222-1645 | 131-749 |
| Mean (days) | 766.27 | 1110.29 | 615.38 |
| Std. Dev. (days) | 920.06 | 1118.86 | 770.75 |

A comparison of episode duration between ORT episodes with no benzodiazepine co-prescription and episodes of ORT with benzodiazepine co-prescription by linear regression with adjustment for age and sex found the coefficient for a benzodiazepine episode was 540.58 days (95% CI 528.56 to 552.61days). This indicates that treatment episodes are around 541 days longer (i.e. retention in treatment better) when there is benzodiazepine co-prescription than episodes with ORT alone after adjustment for age and sex of the person receiving treatment.

***Model Refinement and Sensitivity Analysis***

We considered the possibility that there may be some dilution of the model due to inclusion of non-ORT opiates e.g. for pain or the use chlordiazepoxide for alcohol detoxification. Frequencies of prescriptions for these drugs are:

- Chlordiazepoxide: 0.2% of all prescriptions, and 0.841% of all benzodiazepine prescriptions, 6.5% of patients were ever prescribed this.
- Temgesic: 0.03% of prescriptions, and 0.30% analgesic opioid prescriptions, 0.56% of patients were ever prescribed this.
- Buprenorphine patches: 0.10% of all prescriptions, and 0.92% of all analgesic opioid prescriptions, were for buprenorphine patches. 0.6% of patients were ever prescribed buprenorphine patches.

We concluded that Temgesic and buprenorphine patches were present in very small percentage of opioid prescriptions and patients and are therefore unlikely to affect the model. Chlordiazepoxide represented less than 1% of BZD prescriptions, however it was present in 6.5% of patients.

Further sensitivity analyses were conducted to test the effects of varying the time periods used to define continuous treatment episodes for ORT (100 days in main analysis but varied to 365 days here) and continuous treatment episodes for benzodiazepine (40 days for main and analysis but varied to 60 and 28 days here). The results shown in table 5 are from cox regression analyses and are adjusted for the same covariates as the main analyses. The analysis found the association between benzodiazepine co-prescription and increased hazard for mortality was robust to variations in the time frame used to define continuous treatment episodes. When either the time frame for benzodiazepine or ORT continuous treatment was extended then the hazard ratio between groups was larger. When both were extended at the same time this was not the case.

**Table 5 Sensitivity analyses**

| All cause mortality | | | | | |
|---|---|---|---|---|---|
| ORT duration | BZD duration | Hazard ratio | p | 95% Conf. Interval | |
| 100 | 60 | 1.41 | <0.001 | 1.33 | 1.49 |
| 100 | 28 | 1.17 | <0.001 | 1.10 | 1.25 |
| 365 | 60 | 1.17 | <0.001 | 1.10 | 1.24 |
| 365 | 28 | 1.58 | <0.001 | 1.49 | 1.69 |
| Drug related deaths | | | | | |
| 100 | 60 | 1.39 | <0.001 | 1.27 | 1.51 |
| 100 | 28 | 1.17 | <0.001 | 1.08 | 1.26 |
| 365 | 60 | 1.13 | <0.001 | 1.04 | 1.22 |
| 365 | 28 | 1.55 | <0.001 | 1.42 | 1.69 |
| Non-drug-related deaths | | | | | |
| 100 | 60 | 1.42 | <0.001 | 1.30 | 1.54 |
| 100 | 28 | 1.17 | <0.001 | 1.08 | 1.26 |
| 365 | 60 | 1.20 | <0.001 | 1.11 | 1.30 |
| 365 | 28 | 1.60 | <0.001 | 1.46 | 1.74 |

## DISCUSSION

### *Summary of main findings*

Findings indicated an increased risk of ACM, drug related death and non-drug related death in our cohort when comparing those co-prescribed a benzodiazepine compared to ORT with no prescribed benzodiazepine exposure. However, when analysed by ORT drug, methadone with a co-prescribed benzodiazepine increased hazard of ACM whereas buprenorphine plus a co-prescribed benzodiazepine did not. Retention in treatment was increased when co-prescribed a benzodiazepine alongside ORT compared to ORT alone.

The increased risk of co-prescribing opiates and benzodiazepines are well documented in a range of clinical groups covering opiates for analgesia (30) and in veterans (31). These studies highlight the

significant increased risk of overdose (30) and overdose death (31,32). Our study focussed on those with a history of using illicit substances who are at increased risk of premature mortality without treatment (1). Given the increasing literature specifically covering the ORT population who also use benzodiazepines, it has been possible to compare findings against the international literature.

The ACM hazard ratio for combined ORT (methadone and buprenorphine) concurs with the international literature although the risk in this study appears to be lower (17% increase of ACM, 14% for DRD and 19% for non-drug death) than in other studies of equivalent size and methodological approach (range 70-90% for ACM). (13, 15, 16) There was a higher level of non-drug related death than drug related death within ACM which is indicative of other risks being posed by benzodiazepine use. This group of drugs, indeed sedatives in general, have long been known to increase risk of accidents and falls so this finding could reflect this general risk associated with this drug group. It is possible that the association we have found is due to residual confounding however, a number of other studies have found larger effect sizes for the association between BZD co-prescribing and ACM after adjusting for a greater range of potential confounders. For example Abrahamsson and colleagues (13) controlled for sex, age, previous non-fatal overdose, previous psychiatric in-patient treatment, previous suicide attempt and ORT status and found a HR of 1.75 (1.28-2.39).

This study was able to compare ACM by ORT drug. Analysis did not find evidence of increased risk of ACM among patients prescribed buprenorphine. One study in the literature looked specifically at buprenorphine ACM and whilst there was an increased risk (HR 1.9) (15) this is lower than for the studies that combined ORT drugs or looked at methadone alone. Taken together these findings suggest that buprenorphine poses less risk in combination with a benzodiazepine. This may be because buprenorphine causes less respiratory depression than methadone (33). There may, however, be bias in treatment allocation to methadone or buprenorphine as people who are prescribed methadone could have particular characteristics which pre-dispose them to increased risk of harm. Methadone is associated with more sedation than buprenorphine (34) which is welcomed by some compared to the 'clear headedness' that buprenorphine provides (35). Buprenorphine is a partial agonist in relation to respiratory depression in humans. A detailed pharmacological review concluded that there is a favourable safety profile with less sedation, respiratory depression and potentially less immunosuppression than other opioids and is not impacted by renal disease (36). In addition, it is possible that the smaller number of participants in buprenorphine-only sample, reduced the statistical power to detect effects of co-prescription in this group.

Retention in treatment was significantly longer for those with a benzodiazepine co-prescription than those on ORT alone. This finding concurs with the literature (37). Evidence strongly implies that treatment is protective of overdose (1), therefore keeping people in contact with treatment services, and avoiding unplanned discharge is generally considered protective. The sensitivity analysis found extending the period of ORT (365 day compared to 100 days) and benzodiazepine prescribing (60 days compared to 40 days) reduced the relative effect of benzodiazepine prescription on ACM. This could be because increasing the time window for both benzodiazepine and ORT prescription means we include more people who have disengaged from treatment within the analysis meaning the

baseline risk increases and therefore there is less of an effect of co-prescription. This interpretation requires further research to confirm or refute.

Overall the effect size was lower than other studies in the literature. To explore this we undertook further sensitivity analysis. Firstly we considered if there had been a dilution effect e.g. due to opiate drugs for non ORT purposes, specifically Temgesic[R] and buprenorphine patches, prescribed for pain. In addition we considered the potential inclusion of chlordiazepoxide for alcohol detoxification. However these formed a very small percentage (<1%) of all prescriptions and cases so were not considered to have affected the findings. Therefore we can conclude that whilst there is a raised ACM overall, Scotland appears to have a lower HR ACM compared to other countries. This may well be a factor related to the characteristics of the Scottish treatment population. For example we have high levels of mental and physical co-morbidity in the Scottish drug using population (38) . Brands et al also noted the different clinical profile in people who use BZD highlighting there are more women and more psychiatric conditions. In other words, this is evidence that benzodiazepine and opiate users have more co-morbid risk. (39) This was not specifically tested in our analysis but would be an important plausible explanation given the known high levels of co-occurring mental health problems (40).

There is also a high level of other drugs (as well as benzodiazepines) implicated in DRD in Scotland, which has increased over time, specifically gabapentinoids, cocaine and alcohol are all relatively frequently implicated. This is indicative of a higher risk pattern of drug use in this population. It may be that the many in the ORT group were also using street benzodiazepines so were already exposed to increased risk.

***Methodological Considerations***

A strength of this analysis is the large and inclusive population approach that included the whole ORT treatment population over 10 years. Compared to the existing literature this study is one of the larger studies conducted. The analysis has not considered dose of ORT, or benzodiazepine, which will be variable within individuals over time.

There are some important caveats to this analysis that must be taken into consideration in any further reporting or referencing of this work. This is a treatment population and does not compare ACM for those prescribed a benzodiazepine and ORT with those not receiving a prescribed benzodiazepine and a prescribed ORT i.e. those still using street drugs. The risk of ACM for people who are using non-medical opioids, from a recent meta-analysis is a standardised mortality ratio of 10 (95% CI, 7.6-13.2) (40). This does not account for benzodiazepine prescribing.

***Clinical Implications***

Clinicians need to asses the risks to patients of being exposed to the street market of illicit drugs and the impact of a controlled prescribed alternative, recognising that street benzodiazepines will still be available. Overall improved retention in treatment is an important clinical consideration. ORT reduces the spread of blood borne virus and injecting injuries (as well as criminal activity)(11) and engaging people in ORT longer will reduce overall harm. Retaining people also using benzodiazepines alongside ORT in treatment for longer provides opportunities to address comorbidities and other factors that may contribute to street benzodiazepine use. However, it is

acknowledged that maintenance prescribing of benzodiazepines is 'off-label' in the UK. Clinical decision making should consider other substances an individual may also take alongside their mental and physical health.

*Conclusion*

In the absence of a randomised controlled trial for definitive evidence of risk versus benefit, treatment planning should consider risk on an individual basis. Risk of benzodiazepine co-prescription needs to be balanced against the risk from illicit benzodiazepines and unplanned treatment discontinuation. A randomised controlled trial is urgently needed.

**Contributorship statement**

CM & JS (leads) JR, TR, FC, JD, CD, KK, CW conceptualised the study, CB (lead) managed data and conducted analysis, drafted results and methods sections. CM drafted introduction and discussion. All authors revised drafts to refine interpretation and for intellectual content. CM & JS managed the project.

**Declarations of competing interest**:
Competing interests: All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/disclosure-of-interest/ and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work. TR received honoraria from Camurus for educational inputs in the last 3 years.

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**Data sharing statement**

Data may be obtained from a third party , Public Health Scotland, and are not publicly available.

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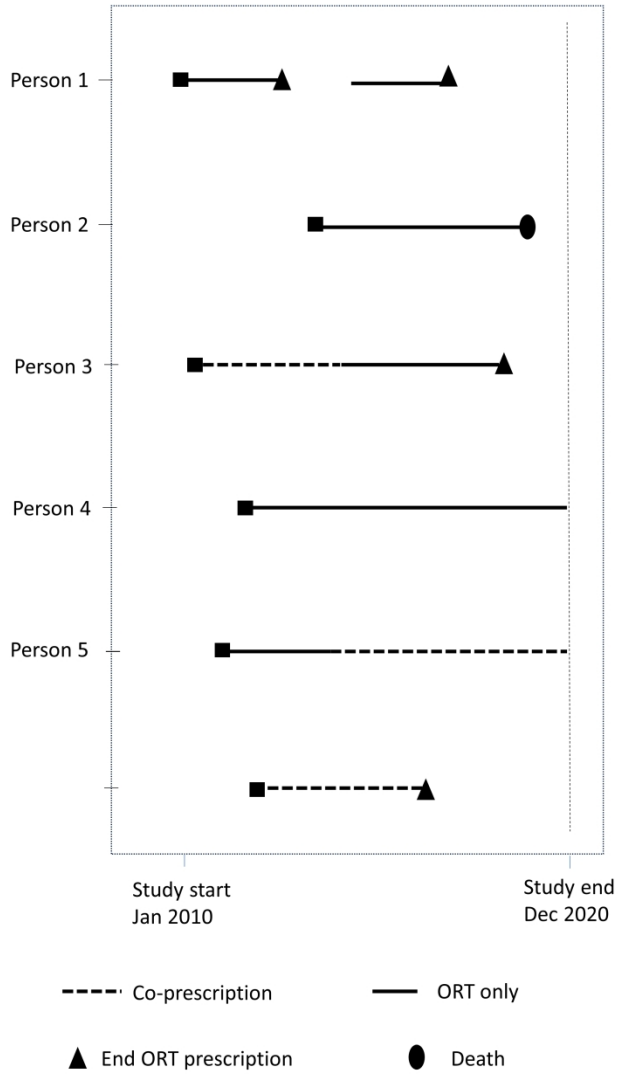


Figure 1 Time to event analysis- lines denote time in study for each participant.

190x338mm (300 x 300 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

| | Item No | Recommendation | Page No |
|---|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | Title & Abstract page 1 &2 |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | Title & Abstract page 1 &2 |
| **Introduction** | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | 3-4 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | 3-4 |
| **Methods** | | | |
| Study design | 4 | Present key elements of study design early in the paper | 4-5 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 5-6 |
| Participants | 6 | (*a*) Give the eligibility criteria, and the sources and methods of selection of participants | 5 |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 6 |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | *6* |
| Bias | 9 | Describe any efforts to address potential sources of bias | 6 |
| Study size | 10 | Explain how the study size was arrived at | 6 |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 6 |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | 6 |
| | | (*b*) Describe any methods used to examine subgroups and interactions | 6 |
| | | (*c*) Explain how missing data were addressed | NA |
| | | (*d*) If applicable, describe analytical methods taking account of sampling strategy | NA |
| | | (*e*) Describe any sensitivity analyses | 7 |
| **Results** | | | |
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | 7 |
| | | (b) Give reasons for non-participation at each stage | |
| | | (c) Consider use of a flow diagram | |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | 7, Table 1 |
| | | (b) Indicate number of participants with missing data for each variable of interest | Table 1 |

| | | | |
|---|---|---|---|
| Outcome data | 15* | Report numbers of outcome events or summary measures | 8 |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | 9 |
| | | (*b*) Report category boundaries when continuous variables were categorized | NA |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | 9 |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | 12 |
| **Discussion** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | 13 |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | 13 |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | 13 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | 13 |
| **Other information** | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | Title page |

*Give information separately for exposed and unexposed groups.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.