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

Catherine Susan Best ,[1] Catriona Matheson,[2] James Robertson,[3,4] Trina Ritchie ,[5] Fiona Cowden,[6] Josh Dumbrell,[2] Clare Duncan,[7] Karthigayan Kessavalou,[7] Caroline Woolston,[7] Joe Schofield [8]

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For numbered affiliations see end of article.

Correspondence to
Catherine Susan Best;
catherine.best2@stir.ac.uk

ABSTRACT

Objective To investigate the association between opioid replacement therapy (ORT) and benzodiazepine (BZD) coprescription and all-cause mortality compared with 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 46 899 participants died: 1398 while on coprescription and 4378 while on ORT only. The mortality per 100 person years was 3.11 during coprescription and 2.34 on ORT only. The adjusted HR for all-cause mortality was 1.17 (1.10 to 1.24). The adjusted HR 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 Coprescription of BZDs in ORT was associated with an increased risk of all-cause mortality, although with a small effect size than the international literature. Coprescribing was also associated with longer retention in treatment. Risk from BZD coprescription needs to be balanced against the risk from illicit BZDs and unplanned treatment discontinuation. A randomised controlled trial is urgently needed to provide a clear clinical direction.

Trial registration number NCT04622995.

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 (BZD), 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 BZD coprescription and mortality cannot be assumed to be causal.

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 (BZDs) 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 BZDs is clear. In 2008, BZDs were implicated in 26% (n=149) of drug-related deaths (DRDs) and were mainly drugs licensed for prescription such as diazepam. By 2018, BZDs and BZD-type drugs were implicated in 67% (792) of DRDs, reducing slightly to 57% in 2022.[3] BZDs identified are predominately substances not licensed for prescription in the UK such as etizolam (a thenodiazepine), but there is an ongoing trend of novel BZDs emerging.[5]

People who use non-prescription BZDs, of unknown constituents and potency, can consume 'megadoses' of BZDs 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 BZD use in the month prior to assessment, an average of 2561 (29%) per year in a 5 year period.[7] The prevalence of illicit BZD 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 BZD 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' BZD use alongside opiate use.[11] While some addiction services are now exploring maintenance prescribing to reduce the risks associated with illicit BZD 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.[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 (ACM), four recorded coprescription to be associated with an increased risk.[13–16] However, of the seven studies that looked at retention in treatment, there were favourable findings in three studies with those coprescribed a BZD with ORT remaining in treatment longer.[14 16 17] There was 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 BZD use among ORT patients receiving methadone found prescribed BZD improved treatment retention, whereas non-prescribed BZD (ie, street drug use) was predictive of treatment drop out.[21] Thus, there are opposing risks and benefits associated with BZD prescribing for those receiving ORT. Much of the existing evidence is based on large epidemiological studies of administrative prescribing and outcome data sets. However, the follow-up time for many of these studies is limited and it is important to understand the longer-term implications of coprescription. Given the particular problems highlighted in Scotland, this study sought to further understand patterns of, and outcomes from BZD 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 1 January 2010 until the time they were known to have died, or until 31 December 2020.

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

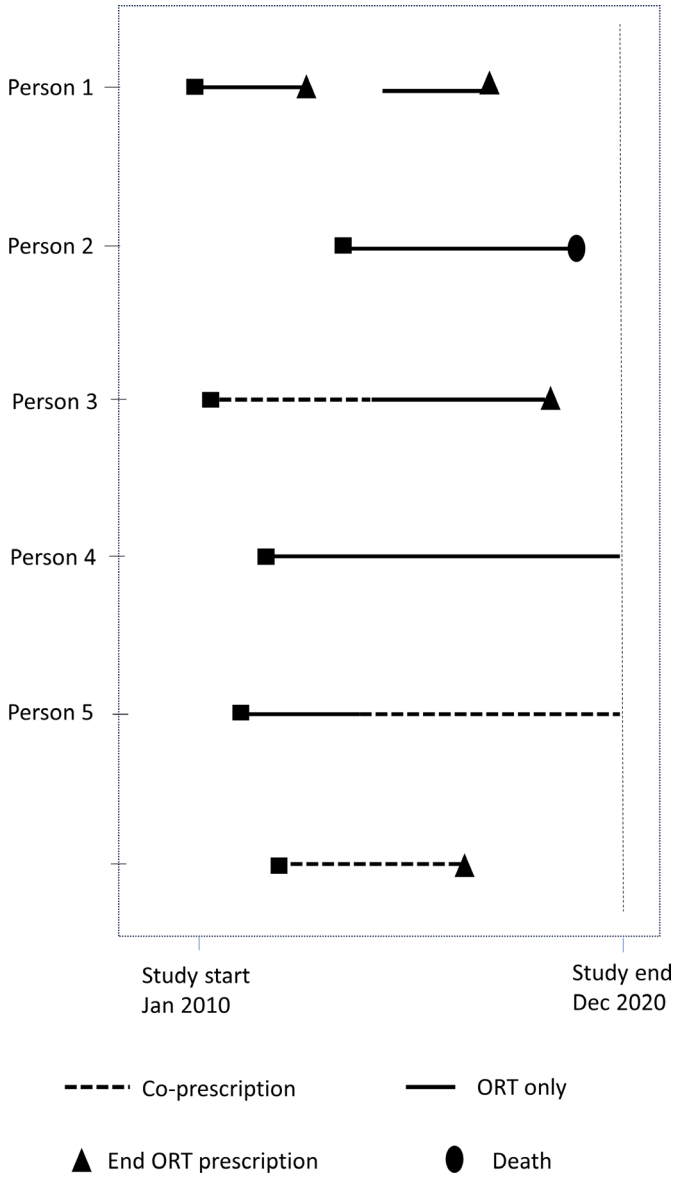

Figure 1 Time to event analysis. ORT, opioid replacement therapy.

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 1 January 2010 and 31 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 and Counter Fraud Services Division who are responsible for the processing and pricing of all prescriptions dispensed in Scotland. General practitioners 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 data set 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 data set. 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 BZDs included

ORT drugs included methadone and buprenorphine. BZDs 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 BZD. The time of 40 days was defined empirically as the time window that captured the majority of inter-prescription time periods for repeat BZD 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 coprescription of ORT and a BZD compared with 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: ACM, DRDs and non-DRDs. Effect sizes are presented as HRs and their 95% CIs.

In secondary analyses, we examined a different definition of the exposure: any prescription of BZD during the study period. That is, we examined whether any prescription of a BZD during the study period was associated with increased mortality. This was done by including BZD 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 with episodes of coprescription with a BZD. 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 data set, we performed sensitivity analyses varying the time window for defining being on ORT treatment and for the exposure that is, BZD coprescription. If the effect of coprescription 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 V.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 DRD. 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

Table 1 Sociodemographic characteristics of cohort

	Any BZD (exposed)	No BZD (unexposed)	Full sample	P value
N	27 184	21 404	48 588	
Sex				
Male	17 155 (63.11%)	15 451 (72.19%)	32 606 (67.11%)	<0.001
Female	10 029 (36.89%)	5953 (27.81%)	15 982 (32.89%)	
SIMD decile				
1 (highest deprivation)	8811 (32.41%)	7055 (32.96%)	15 866 (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	13 359 (49.14%)	10 249 (47.88%)	23 608 (48.59%)	0.689
Other urban areas	9516 (35.01%)	7746 (36.19%)	17 262 (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%)	

BZD, benzodiazepine; SIMD, Scottish Index of Multiple Deprivation.

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.

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 48 588 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 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 BZD prescription at some time between January 2010 and December 2020. Sociodemographics 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 BZD compared with men (62.8% of females, 52.6% of males on BZD) which was statistically significant (χ^2=447, df=1, p<0.001). There was no association between exposure and either social deprivation or urbanicity.

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

During follow-up, 5776 participants died: 1398 while on coprescription of a BZD and ORT and 4378 while on ORT only. The total time spent in the study for all participants was 232 282 years. The total time in the study while on BZD prescription and ORT was 45 046 years (mean per participant 2.21 years, median per participant 1.09 years) and the total time on ORT was only 187 236 years (mean per participant 4.09, median per participant 3.36 years). The mortality per 100 person years was 3.11 during coprescription and 2.34 on ORT only.

Table 2 Effect of coprescription of a BZD on outcomes in people receiving opioid replacement therapy

Outcome	HR*	P value	95% CI
All-cause mortality	1.17	<0.001	1.10 to 1.24
Drug-related death	1.14	0.003	1.04 to 1.24
Not drug-related death	1.19	<0.001	1.09 to 1.30

*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.
BZD, benzodiazepine; ORT, opioid replacement therapy.

This section outlines the results of three Cox regressions examining the effect of coprescription of BZDs on the outcomes: ACM, DRDs and deaths not classified as drug related.

The total number of participants included in the Cox regression analysis was 46 899. There were 5776 deaths from any cause during the time period. Of these, 2938 were DRDs and 2838 were not classified as DRDs.

Table 2 shows the HR and 95% CI for the effect of BZD coprescription versus ORT only on the three mortality outcomes.

After adjustment, the effect of exposure (coprescription of BZDs in the last 40 days) increased the hazard for ACM relative to ORT alone, by 17% (HR 1.17; 95% CI, 1.10 to 1.24) it increased the hazard for DRD 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

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 shows that methadone with a coprescribed BZD was associated with an increase hazard of ACM compared with methadone alone, whereas buprenorphine plus coprescribed BZDs was not associated with an increased hazard for ACM.

Table 3 Comparison of results with methadone versus buprenorphine opioid prescription

ORT definition	HR	P value	95% CI
Methadone	1.41	<0.001	1.32 to 1.50
Buprenorphine	1.16	0.189	0.93 to 1.44

ORT, opioid replacement therapy.

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 BZD.

A comparison of episode duration between ORT episodes with no BZD coprescription and episodes of ORT with BZD coprescription by linear regression with adjustment for age and sex found the coefficient for a BZD episode was 540.58 days (95% CI, 528.56 to 552.61 days). This indicates that treatment episodes are around 541 days longer (ie, retention in treatment better), when there is BZD coprescription 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 for example, for pain or the use chlordiazepoxide for alcohol detoxification. Frequencies of prescriptions for these drugs are as follows:

- Chlordiazepoxide: 0.2% of all prescriptions, and 0.841% of all BZD 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 BZD (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 BZD coprescription 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 BZD or ORT continuous treatment was extended, then the HR between groups was larger. When both were extended at the same time, this was not the case.

DISCUSSION

Summary of main findings

Findings indicated an increased risk of ACM, DRD and non-DRD in our cohort when comparing those coprescribed

Table 4 Treatment episode length for ORT episodes with and without a BZD coprescription

	All ORT episodes	ORT with any BZD coprescription	ORT with no BZD prescriptions
N episodes	121 435	37 022	84 413
Median (days)	375	678	312
IQR (days)	153–1005	222–1645	131–749
Mean (days)	766.27	1110.29	615.38
SD (days)	920.06	1118.86	770.75

BZD, benzodiazepine; ORT, opioid replacement therapy.

a BZD compared with ORT with no prescribed BZD exposure. However, when analysed by ORT drug, methadone with a coprescribed BZD increased hazard of ACM, whereas buprenorphine plus a coprescribed BZD did not. Retention in treatment was increased when coprescribed a BZD alongside ORT compared with ORT alone.

The increased risk of coprescribing opiates and BZDs are well documented in a range of clinical groups covering opiates for analgesia[29] and in veterans.[30] These studies highlight the significant increased risk of overdose[29] and overdose death.[30 31] Our study focused 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 BZDs, it has been possible to compare findings against the international literature.

The ACM HR 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 17] There was a higher level of non-DRD than DRD within ACM which is indicative of other risks being posed by BZD use. This group of drugs, indeed sedatives in general, has 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 coprescribing 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 while there was an increased risk (HR 1.9),[17] 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

Table 5 Sensitivity analyses

All cause mortality				
ORT duration	**BZD duration**	**HR**	**P value**	**95% CI**
100	60	1.41	<0.001	1.33 to 1.49
100	28	1.17	<0.001	1.10 to 1.25
365	60	1.17	<0.001	1.10 to 1.24
365	28	1.58	<0.001	1.49 to 1.69
Drug-related deaths				
100	60	1.39	<0.001	1.27 to 1.51
100	28	1.17	<0.001	1.08 to 1.26
365	60	1.13	<0.001	1.04 to 1.22
365	28	1.55	<0.001	1.42 to 1.69
Non-drug-related deaths				
100	60	1.42	<0.001	1.30 to 1.54
100	28	1.17	<0.001	1.08 to 1.26
365	60	1.20	<0.001	1.11 to 1.30
365	28	1.60	<0.001	1.46 to 1.74

BZD, benzodiazepine; ORT, opioid replacement therapy.

a BZD. This may be because buprenorphine causes less respiratory depression than methadone.[32] There may, however, be bias in treatment allocation to methadone or buprenorphine as people who are prescribed methadone could have particular characteristics which predispose them to increased risk of harm. Methadone is associated with more sedation than buprenorphine,[33] which is welcomed by some compared with the 'clear headedness' that buprenorphine provides.[34] 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.[35] In addition, it is possible that the smaller number of participants in buprenorphine-only sample, reduced the statistical power to detect effects of coprescription in this group.

Retention in treatment was significantly longer for those with a BZD coprescription than those on ORT alone. This finding concurs with the literature.[36] 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 with 100 days) and BZD prescribing (60 days compared with 40 days) reduced the relative effect of BZD prescription on ACM. This could be because increasing the time window for both BZD 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 coprescription. 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. First, we considered if there had been a dilution effect for example, due to opiate drugs for non ORT purposes, specifically Temgesic 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 while there is a raised ACM overall, Scotland appears to have a lower HR ACM compared with 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 comorbidity in the Scottish drug using population.[37] Brands *et al* also noted the different clinical profile in people who use BZD, highlighting that there are more women and more psychiatric conditions. In other words, this is evidence that BZD and opiate users have more comorbid risk.[38] 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.[39]

There is also a high level of other drugs (as well as BZDs) 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 BZDs 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 with the existing literature, this study is one of the larger studies conducted. The analysis has not considered dose of ORT, or BZD, 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 BZD and ORT with those not receiving a prescribed BZD and a prescribed ORT, that is, 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 to 13.2).[39] This does not account for BZD 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 BZDs 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 BZDs alongside ORT in treatment for longer provides opportunities to address comorbidities and other factors that may contribute to street BZD use. However, it is acknowledged that maintenance prescribing of BZDs 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 BZD coprescription needs to be balanced against the risk from illicit BZDs and unplanned treatment discontinuation. A randomised controlled trial is urgently needed.

Author affiliations
[1]Faculty of Health Sciences and Sport, University of Stirling, Stirling, UK
[2]University of Stirling, Stirling, UK
[3]Muirhouse Medical Group, Edinburgh, UK
[4]University of Edinburgh, Usher Institute, Edinburgh, UK
[5]NHS Greater Glasgow and Clyde, Glasgow, UK

[6]NHS Tayside, Dundee, UK
[7]NHS Ayrshire and Arran, Ayr, UK
[8]School of Health in Social Science, The University of Edinburgh College of Humanities and Social Science, Edinburgh, UK

Twitter Catherine Susan Best @cathbest, Catriona Matheson @catrionaMath and Trina Ritchie @trinaritchie

Contributors CM and JS (leads) JR, TR, FC, JD, CD, KK and CW conceptualised the study, CSB (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 and JS managed the project. CSB is the guarantor.

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ORCID iDs
Catherine Susan Best http://orcid.org/0000-0002-3652-2498
Trina Ritchie http://orcid.org/0000-0002-5409-700X
Joe Schofield http://orcid.org/0000-0002-1307-2375

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