Ageing opioid users' increased risk of methadone-specific death in the UK

Citation for published version:
Pierce, M, Millar, T, Robertson, JR & Bird, SM 2018, 'Ageing opioid users' increased risk of methadone-specific death in the UK', *International Journal of Drug Policy*, vol. 55, pp. 121-127.
https://doi.org/10.1016/j.drugpo.2018.02.005

Digital Object Identifier (DOI):
10.1016/j.drugpo.2018.02.005

Link:
Link to publication record in Edinburgh Research Explorer

Document Version:
Publisher's PDF, also known as Version of record

Published In:
International Journal of Drug Policy

Publisher Rights Statement:
0955-3959/ © 2018 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY license (http://creativecommons.org/licenses/BY/4.0/).

General rights
Copyright for the publications made accessible via the Edinburgh Research Explorer is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy
The University of Edinburgh has made every reasonable effort to ensure that Edinburgh Research Explorer content complies with UK legislation. If you believe that the public display of this file breaches copyright please contact openaccess@ed.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.
Research Paper

Ageing opioid users’ increased risk of methadone-specific death in the UK

Matthias Pierce, Tim Millar, J. Roy Robertson, Sheila M. Bird

A Centre for Biostatistics, School of Health Sciences, University of Manchester, Manchester M13 9PL, United Kingdom
b Centre for Mental Health and Safety, School of Health Sciences, University of Manchester, Manchester M13 9PL, United Kingdom
c Usher Institute of Population Health Sciences and Informatics, University of Edinburgh, Edinburgh EH16 4UX, United Kingdom
d Centre for Biostatistics, School of Health Sciences, University of Manchester, Manchester M13 9PL, United Kingdom

ABSTRACT

Background: The first evidence that the hazard ratio (HR) for methadone-specific death rises more steeply with age-group than for all drug-related deaths (DRDs) came from Scotland’s cohort of 33,000 methadone-prescription clients. We aim to examine, for England, whether illicit opioid users’ risk of methadone-specific death increases with age; and to pool age-related HRs for methadone-specific deaths with those for Scotland’s methadone-prescription clients.

Methods: The setting is all services in England that provide publicly-funded, structured treatment for illicit opioid users, the methodology linkage of the English National Drug Treatment Monitoring System and mortality database, and key measurements are DRDs, methadone-specific DRDs, or heroin-specific DRDs, by age-group and gender, with proportional hazards adjustment for substances used, injecting status and periods in/out of treatment.

Results: Linkage was achieved for 129,979 adults receiving prescribing treatment modalities for opioid dependence during April 2005 to March 2009 and followed-up for 378,009 person-years (pys).

There were 1,266 DRDs: 271 methadone-specific (7 per 10,000 pys: irrespective of gender) and 473 heroin-specific (15 per 10,000 pys for males, 7 for females). Methadone-specific DRD-rate per 10,000 person-years was 3.5 (95% CI: 2.7–4.4) at 18–34 years, 8.9 (CI: 7.3–10.5) at 35–44 years and 18 (CI: 13.8–21.2) at 45+ years; heroin-specific DRD-rate was unchanged with age.

Relative to 25–34 years, pooled HRs for UK clients’ methadone-specific deaths were: 0.87 at < 25 years (95% CI: 0.56–1.35); 2.14 at 35–44 years (95% CI: 1.76–2.60); 3.75 at 45+ years (95% CI: 2.99–4.70).

Conclusion: International testing and explanation are needed of UK’s sharp age-related increase in the risk of methadone-specific death. Clients should be alerted that their risk of methadone-specific death increases as they age.

What is known already

- Record-linkage studies internationally have shown the value of opioid substitution therapy as a treatment which reduces substantially clients’ risk of drug-related death (DRD); also that DRD-rates are lower for female opioid users and increase with age beyond 35 years but that the female advantage is much reduced for older clients.
- Despite harm reduction measures, such as opioid substitution therapy, UK’s DRDs have increased markedly in the past decade, in a strongly age-related manner.
- One powerful record-linkage study on Scotland’s methadone-prescription clients in 2009–2013 has shown that their adjusted hazard ratios for methadone-specific DRD increased sharply by age-group, irrespective of gender.

What this study adds

- By analysing the opioid-specificity of deaths for England’s National Drug Treatment Monitoring System (NDTMS) cohort of nearly 130,000 opioid users who started a prescribing treatment modality, predominantly methadone, during 1 April 2005 to 31 March 2009, we confirmed that their hazard ratios for methadone-specific DRDs also increased sharply by age-group.
- Importantly, nearly half of the cohort’s person-years were aged 35+ years; and age-effects persisted after adjustment for risk-behaviours.

https://doi.org/10.1016/j.drugpo.2018.02.005
Received 23 August 2017; Received in revised form 15 January 2018; Accepted 12 February 2018
0955-3959/ © 2018 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).
• By pooling results from the two major UK studies, we showed that opioid-dependent clients’ hazard ratio for methadone-specific death nearly doubled at 35–44 years (compared with 25–34 years); and quadrupled at 45+ years.

Introduction

In the past decade, record-linkage studies in the UK and internationally have not only shown the value of opioid substitution therapy as a treatment which reduces substantially clients’ risk of drug-related death (DRD), by half (95% CI: 0.38 to 0.51) for those with a history of injecting (Pierce et al., 2016); but also that DRD-rates are lower for female opioid users; increase with age beyond 35 years; and yet the female advantage is reduced for older clients (Bird, Robertson, & Strang, 2010; Cornish, Macleod, Strang, Vickerman, & Hickman, 2010; Cousins et al. 2011; Degenhardt et al., 2011; Kimber et al., 2010; King, Bird, Overstall, Hay, & Hutchinson, 2013; King, Bird, Overstall, Hay, & Hutchinson, 2014; Merral et al. 2012; Pierce et al., 2016; Pierce, Bird, Hickman, & Millar, 2015; Strang, Hall, Hickman, & Bird, 2010).

To assess the role of prescribed methadone in explaining the above demographic influences, Gao et al. (2016) considered age-group and gender, in addition to prescription source (general practitioner, other-source) and quintile for the quantity of prescribed methadone, as being potentially informative about the 361 methadone-specific DRDs experienced by 33,000 methadone-prescription clients in Scotland during 121,000 person-years of follow-up in 2009 to 2013. Their analysis revealed a steeply increased hazard by age-group, irrespective of gender (which was not prognostic) and that the top quintile for the baseline quantity of prescribed methadone conferred additional hazard for methadone-specific DRDs.

Relative to 25–34 year olds in the Scottish methadone-prescription cohort, the adjusted hazard ratio (HR) for methadone-specific deaths was 0.5 (95% CI: 0.3–1.0) for those aged under 25 years, 1.9 (95% CI: 1.5–2.4) at 35–44 years and 2.9 (95% CI: 2.2–3.9) at 45+ years of age. Eleven percent of Scotland’s methadone-prescription clients were aged 45+ years.

The first to demonstrate how steeply the risk of methadone-specific death increases with client-age, Scotland’s methadone-prescription cohort had the advantage of a national protocol in Scotland for toxicological reporting at forensic autopsy so that the specified opioids were implicated in, not merely present at, DRD. However, substantial numbers of Scotland’s two million methadone prescriptions issued over four years lacked a Community-Health Index (CHI)-number, meaning that they were not readily linkable to individual clients. For that reason, Scottish clients’ periods on/off prescribed methadone could not be analysed (Gao et al., 2016). Nonetheless, an estimated 82% of Scotland’s methadone clients were linkable to mortality-records because they had at least one CHI-identified prescription (Gao et al., 2016).

Besides calling for a better understanding of methadone’s pharmacodynamics in older clients, many with potential confounders such as progressive physical or mental ill-health, Gao et al. (2016) noted that, since 2006, electrocardiograms have been recommended by UK’s Medicines and Healthcare products Regulatory Authority for older or persistent methadone clients on higher doses. This recommendation was made to detect prolongation of that part of the heart’s normal electrical cycle known as the QT interval because, unlike buprenorphine, methadone – alone and with other drugs commonly used for comorbidities, especially mental health conditions: antidepressants, antipsychotics, antibiotics (macrolides, quinolones, azoles), antiarhythmic, protease inhibitors and the loop diuretic furosemide (Romero et al., 2016) – is known to prolong the QT interval; and prolongation increases the risk of torsades de pointes and sudden cardiac death, yet leaves no detectable trace at autopsy. Other risk factors for corrected QT prolongation include age-related co-morbidities such as renal impairment, heart or liver disease; and being female, see Gao et al. (2016).

Before diving too deeply into confounders, as above, in explanation for the strongly age-related increase in Scottish clients’ hazard of methadone-specific death, we considered that it was important first to test the Scottish results. England’s National Drug Treatment Monitoring System (NDTMS) cohort of nearly 130,000 opioid users who had started a prescribing treatment modality during 1 April 2005 to 31 March 2009 enabled such testing. The calendar period for the NDTMS cohort was immediately preceding Scotland’s (Pierce et al. 2016), thereby also preceding the heroin drought of 2010; 47% of the NDTMS cohort’s person-years were aged 35+ years, similar to 48% at baseline for Scotland’s methadone-prescription cohort. Importantly, information on NDTMS clients’ periods in/out of treatment, declared injecting and misuse of alcohol, benzodiazepines and other drugs (Pierce et al. 2016) could be taken into account in addition to age-group and gender. The English cohort’s gender and age-specific mortality from causes other than DRDs has been reported elsewhere (Pierce et al., 2015).

In this paper, for NDTMS opioid-user clients who received at least one day of opioid agonist prescribing (OAP), we aimed to:

i) document the influence of demographic risk factors (age-group; gender) on OAP clients’ HR for DRD, methadone-specific DRD, heroin-specific DRD, having adjusted also for clients’ time-dependent declared injecting (ever) and past-month misuse of alcohol, benzodiazepines, and other drugs;
ii) repeat the above analysis with adjustment also for periods in/out of treatment;
iii) pool age-related HRs for methadone-specific deaths from the Scotland’s methadone-prescription cohort and England’s OAP cohort.

Methods

Data

The National Drug Treatment Monitoring System (NDTMS) provides details on all structured treatment for substance misuse provided in England. The cohort for this national record linkage study was identified from NDTMS records collected over the study period 1st April 2005 to 31st March 2009; with linkage to mortality records provided that the subject’s identifier was not in a many-to-one mapping, see Fig. 1. The Office for National Statistics (ONS) provided data on deaths occurring during the observation period which were registered by 30 September 2011. This allowed for delays in the registration process pending inquest verdicts.

Records in NDTMS are created for each treatment modality received

Fig. 1. Flow diagram of case-selection for the analysis cohort.
by a given patient. Treatment modalities were categorised, as in Pierce et al. (2016) into: OAP; psychosocial treatment; and residential treatment. A treatment episode is defined as an unbroken or contiguous series of treatment modalities.

Data were supplied at the episode-level on: self-reported illicit drug injecting status (past month); and an optional self-report of up to three additional problematic psychoactive substances. In NDTMS, prescribed opioid agonist was not differentiated as to methadone or buprenorphine, but the vast majority was methadone (Cornish et al., 2010).

Patients were included in the OAP cohort if they received at least one day of prescribing treatment over the study period and were aged 18 to 64 at their inclusion-date. The cohort analysed here is a sub-cohort of that described by Pierce et al. (2016) who checked thoroughly the proportionality of DRD hazards.

The NDTMS cohort was linked to ONS mortality records. For each death record, the underlying cause of death is coded according to the ICD-10 framework with DRDs defined by ICD-10 codes according to ONS’s definition (Office for National Statistics, 2017). Additionally, for each death, the ONS created flags to indicate whether ‘methadone’ and/or ‘heroin’ and/or ‘buprenorphine’ were mentioned on the death certificate.

In England, the opioid-specificity of DRDs is determined by the drugs which are mentioned on the death-certificate. As the majority of DRDs are registered following a coroner’s inquest, the text on the coroner’s death certificate is used by ONS to code all of the substances involved in the death. Analogous to Gao et al. (2016), we define methadone-specific DRDs as those in which methadone was mentioned but neither heroin nor buprenorphine; and heroin-specific DRDs as those in which heroin was mentioned but neither methadone nor buprenorphine. If opioid was mentioned on a DRD death certificate without further specification, which occurs for around 5% of England’s opioid-related DRDs (Office for National Statistics, 2017), the death was counted as DRD; but neither as methadone-specific DRD nor as heroin-specific DRD. Similarly, any DRD which mentioned buprenorphine was counted as DRD; but neither as methadone-specific DRD nor as heroin-specific DRD. However, buprenorphine is so infrequently mentioned in England and Wales as to be not separately tabulated by ONS even for DRD registrations in 2016.

Treatment and mortality data were linked using a minimal identifier in each database (initials, date of birth, gender) and government region of usual residence. Prior analysis indicated that 22% of minimal identifiers in the treatment population were shared by one or more individuals in the criminal records database which contributed to the cohort’s derivational linkages (Pierce et al., 2016). These minimal identifiers were removed from the analysis cohort because the subject’s drug treatment record could not be reliably linked to his/her mortality record. The resulting OAP cohort comprised in 129,979 linked individuals, see Fig. 1.

Data were rendered anonymous to the research team, via irreversible encryption of identifying information, prior to their release by source organizations.

Statistical analysis

Descriptive life-table analysis (per 10,000 person-years of follow-up) was undertaken for the outcomes: any DRD; DRD that mentioned methadone on the death certificate but neither heroin nor buprenorphine (methadone-specific DRD); and DRD that mentioned heroin on the death certificate but neither methadone nor buprenorphine (heroin-specific DRD).

Subjects entered the risk-set at their earliest OAP-treatment date during the period 1st April 2005 to 31st March 2009. They left the risk set at the earlier of their date of death, 65th birthday, or the end of data collection (31st March 2009).

Time-dependent covariates for the OAP cohort were time-updated age (categorised as 18–24; 25–34, 35–44, 45–64 years) and patient-reported behavioural covariates, collected at the beginning of each treatment episode and defined from their date of first report, namely: injecting status; problematic use of alcohol, benzodiazepines, crack cocaine, cocaine powder and amphetaamines (the latter two substances combined due to a low level of reporting). A time-dependent covariate for being in/out of treatment was also created to indicate whether the patient was enrolled in any structured treatment (prescribing or otherwise) using the start and end dates for treatment modality.

For each outcome, cause-specific Cox proportional hazard ratios were estimated by censoring other deaths and using covariates as above. Interaction between age and gender was anticipated for DRDs (Pierce et al., 2015; King et al., 2013; King et al., 2014).

When pooling the age-related HRs for methadone-specific deaths from the Scottish and English cohorts, age-group specific weights were derived from the information contributed per age-group by each cohort; alternatively, a common weighting was derived from the total information across all three age-groups (< 25 years; 35–44 years; 45+ years). Please see Supplementary Information for details of both calculations. In statistical terms, notice that the information which a cohort contributes about ln HR for a particular age-group (relative to 25–34 year olds) is defined by the reciprocal of the variance of the cohort’s estimated ln HR for that age-group.

Results

England’s OAP cohort of 129,979 prescribing modality clients was followed-up for 378,009 person-years (pys) and experienced 1,266 DRDs, an overall rate of 33 DRDs per 10,000 pys (95% CI: 31.6–35.3), of which 271 were methadone-specific DRDs and 473 were heroin-specific.

Overall, the OAP cohort’s methadone-specific DRD-rate was 7 per 10,000 pys, irrespective of gender. By age-group, however, the methadone-specific DRD-rate was 3.5 (95% CI: 2.7–4.4) at 18–34 years, 8.9 (CI: 7.3–10.5) at 35–44 years and 18 (CI: 13.8–21.2) at 45+ years; whereas the heroin-specific DRD-rate of 12.5 per 10,000 pys was unchanged by age, but was significantly higher for males than females, see Table 1.

None of the behavioural risk-factors in Table 1 had a materially different influence on heroin-specific versus methadone-specific DRDs, apart from having ever injected (a more accentuated HR for heroin-specific deaths). Table 2 shows that the doubling of DRD-risk when out-of-treatment partitions as a nearly quadrupled risk of heroin-specific DRD but non-significant 20% out-of-treatment reduction in methadone-specific DRD risk. Other covariate influences are unchanged from Table 1.

The weights used for the Scottish methadone-prescription cohort in pooling age-group specific HRs (see Introduction for the Scottish results to be pooled) were 43% for under 25 years of age, 63% for 35–44 year olds, and 55% at 45+ years; alternatively, a common weighting of 58% may be preferred, which is based on the sum of information across age-groups. The alternatives agree inferentially, see Supplementary information.

Relative to clients aged 25–34 years, the pooled HRs for methadone-specific deaths across Scotland’s methadone-prescription client cohort and the English prescribing cohort from Table 1 were: under 25 years of age, 0.87 (95% CI: 0.56–1.35); at 35–44 years, 2.14 (95% CI: 1.76–2.60); and at 45+ years, 3.75 (95% CI: 2.99–4.70).

Discussion

Summary of main findings and recommendations

The OAP cohort allowed us to validate, for England, the novel record-linkage findings from Scotland that opioid using clients’ hazard of methadone-specific death rises steeply with age and is independent of gender. In addition, we have shown that these demographic influences
hold up when adjustment is made for a triad of declared behavioural characteristics (injecting, misuse of alcohol and misuse of benzodiazepines) and for periods in/out of opioid substitution therapy, factors not addressed in Scotland’s methadone-prescription cohort.

Next, we pooled age-related HRs from the two national cohorts for added precision so that, relative to 25–34 year olds, the OAP clients’ pooled HRs for methadone-specific deaths in the UK were doubled at 35–44 years and nearly quadrupled at 45+ years.

We therefore recommend that consideration be given to reviewing older clients’ methadone dosage in the context of the patient’s cardiovascular, respiratory and liver or renal related co-morbidities (Gao et al., 2016); and prescribed medications, including for mental health problems (Independent Expert Group, 2017). Gao et al. (2016) recommended that a representative sample of 45+ year old methadone clients be offered electrocardiograms (ECG) to establish what proportion of them (1%, 5% or 10%) had prolongation of their corrected QT segment by 60 milliseconds or to above 500 milliseconds. In the light of our evidence-synthesis, we propose that this surveillance should be extended to 35–44 year olds. We propose surveillance as the initial step to interpret ECGs and yet to be moderated in the UK Government (2017). Importantly, the earlier period preceding the heroin drought of 2010.

Limitations

For different reasons, the availability of unique identifiers limited linkage to about 80% of clients in the OAP cohort, see Fig. 1; and in Scotland’s methadone-client cohort (Gao et al., 2016). As detailed in Methods, we discarded 22% of identifiers from the OAP cohort where there was evidence that two or more individuals might share the same details. Nonetheless, it remains possible that some proportion of the remainder might also have shared details with other individuals in their region. Errors in matching within treatment records and in matching

Table 1

Proportional hazard analysis: DRD, methadone only and heroin only mortality associated with covariates, for opioid users who had a prescribing treatment modality over the period 1st April 2005 to 31st March 2009. (N = 129,979; person-years (pys) = 378,009).

|                | Pys (k) | Deaths | CMR per 10k pys | Adjusted Hazard Ratio [95% CI] | P value | Deaths | CMR per 10k pys | Adjusted Hazard Ratio [95% CI] | P value | Deaths | CMR per 10k pys | Adjusted Hazard Ratio [95% CI] | P value |
|----------------|---------|--------|----------------|-----------------------------|---------|--------|----------------|-----------------------------|---------|--------|----------------|-----------------------------|---------|
| Age            |         |        |                |                            |         |        |                |                            |         |        |                |                            |         |
| 18–24          |         |        |                |                            | < 0.001 | 14     | 4.2            | 1.26 [0.70, 2.27]            | < 0.001 | 36     | 10.7           | 0.99 [0.69, 1.41]            | 0.796   |
| 25–34          |         |        |                |                            | < 0.001 | 57     | 3.4            | REF                         | < 0.001 | 202    | 12.1           | REF                         |         |
| 35–44          |         |        |                |                            | < 0.001 | 115    | 8.9            | 2.60 [1.89, 3.57]           | < 0.001 | 172    | 13.3           | 1.09 [0.89, 1.33]           |         |
| 45+            |         |        |                |                            | < 0.001 | 85     | 17.5           | 5.14 [3.66, 7.21]           | < 0.001 | 63     | 13.0           | 1.11 [0.84, 1.48]           |         |
| Gender         |         |        |                |                            |         |        |                |                            |         |        |                |                            |         |
| Male           |         |        |                |                            | < 0.001 | 188    | 7.3            | REF                         | < 0.001 | 390    | 15.1           | REF                         | < 0.001 |
| Female         |         |        |                |                            | < 0.001 | 83     | 6.9            | 1.09 [0.84, 1.42]           | < 0.001 | 83     | 6.9            | 0.49 [0.38, 0.62]           |         |
| Injecting, never declared |     |        |                |                            |         |        |                |                            |         |        |                |                            |         |
| Yes            |         |        |                |                            | < 0.001 | 130    | 8.8            | 1.64 [1.27, 2.13]           | 0.001   | 277    | 18.8           | 2.47 [2.00, 3.04]            | < 0.001 |
| No             |         |        |                |                            | < 0.001 | 111    | 5.7            | REF                         | < 0.001 | 135    | 6.9            | REF                         |         |
| Declared alcohol misuse | |        |                |                            |         |        |                |                            |         |        |                |                            |         |
| Yes            |         |        |                |                            | < 0.001 | 48     | 10.5           | 1.44 [1.05, 1.98]           | 0.024   | 92     | 20.1           | 1.63 [1.29, 2.05]            | < 0.001 |
| No             |         |        |                |                            | < 0.001 | 223    | 6.7            | REF                         | < 0.001 | 381    | 11.5           | REF                         |         |
| Declared benzoazepine misuse | |        |                |                            |         |        |                |                            |         |        |                |                            |         |
| Yes            |         |        |                |                            | < 0.001 | 54     | 10.0           | 1.44 [1.07, 1.95]           | 0.017   | 95     | 17.6           | 1.34 [1.07, 1.69]            | 0.011   |
| No             |         |        |                |                            | < 0.001 | 217    | 6.7            | REF                         | < 0.001 | 378    | 11.7           | REF                         |         |
| Declared crack cocaine misuse | |        |                |                            |         |        |                |                            |         |        |                |                            |         |
| Yes            |         |        |                |                            | < 0.001 | 76     | 5.6            | 0.69 [0.52, 0.90]           | 0.006   | 170    | 12.4           | 0.91 [0.75, 1.10]            | 0.334   |
| No             |         |        |                |                            | < 0.001 | 195    | 8.1            | REF                         | < 0.001 | 303    | 12.5           | REF                         |         |
| Declared cocaine/amphetamine misuse | |        |                |                            |         |        |                |                            |         |        |                |                            |         |
| Yes            |         |        |                |                            | < 0.001 | 41     | 8.3            | 1.15 [0.82, 1.61]           | 0.420   | 84     | 17.0           | 1.29 [1.01, 1.64]            | 0.038   |
| No             |         |        |                |                            | < 0.001 | 230    | 7.0            | REF                         | < 0.001 | 389    | 11.8           | REF                         |         |

* Evidence for gender and age interaction — DRD model: p = .013; methadone only model: p = .350; heroin only model: p = .062.
these to mortality records might potentially have occurred as a consequence of this but, insofar as these arose due to the random coincidence of the minimal identifying information that was available in the OAP cohort, these errors will have contributed noise to the analysis rather than exerting any systematic effect.

England, and many other countries, does not have a national protocol for toxicology and its reporting at forensic autopsy. Thus, rather than exerting any systematic effect of the minimal identifying information that was available in the OAP cohort:

---

### Table 2

Proportional hazard analysis: DRD, methadone only and heroin only mortality associated with treatment and covariates, for opioid users who had a prescribing treatment modality over the period 1st April 2005 to 31st March 2009. (N = 129,979; person-years (pys) = 378,009).

| Treatment | Pys (k) | Deaths | CMR per 10k pys | Adjusted Hazard Ratio [95% CI]* | P value | Deaths | CMR per 10k pys | Adjusted Hazard Ratio [95% CI]* | P value | Deaths | CMR per 10k pys | Adjusted Hazard Ratio [95% CI]* | P value |
|-----------|---------|--------|----------------|-------------------------------|---------|--------|----------------|-------------------------------|---------|--------|----------------|-------------------------------|---------|
| **In** | 283,801 | 790   | 27.8 | REF | < 0.001 | 217 | 7.6 | REF | 0.122 | 226 | 8.0 | REF | < 0.001 |
| **Out** | 94,298 | 476 | 50.5 | 1.98 [1.76, 2.23] | | 54 | 5.7 | 0.79 [0.58, 1.07] | | 247 | 26.2 | 3.72 [3.09, 4.49] | |
| **Age** | | | | | | | | | | | | | |
| 18–24 | 33,588 | 74 | 22.0 | 0.90 [0.70, 1.15] | < 0.001 | 14 | 4.2 | 1.27 [0.71, 2.28] | < 0.001 | 36 | 10.7 | 0.93 [0.65, 1.33] | 0.379 |
| 25–34 | 167,045 | 429 | 25.7 | REF | | 57 | 3.4 | REF | | 202 | 12.1 | REF | |
| 35–44 | 128,936 | 514 | 39.9 | 1.57 [1.38, 1.78] | | 115 | 8.9 | 2.59 [1.88, 3.56] | | 172 | 13.3 | 1.13 [0.92, 1.39] | |
| 45+ | 48,530 | 249 | 51.3 | 2.18 [1.86, 2.55] | | 85 | 17.5 | 5.08 [3.62, 7.13] | | 63 | 13.0 | 1.22 [0.92, 1.62] | |
| **Gender** | | | | | | | | | | | | | |
| Male | 257,948 | 971 | 37.6 | REF | < 0.001 | 188 | 7.3 | REF | 0.531 | 390 | 15.1 | REF | < 0.001 |
| Female | 120,151 | 295 | 24.6 | 0.74 [0.65, 0.85] | | 83 | 6.9 | 1.09 [0.84, 1.41] | | 83 | 6.9 | 0.52 [0.41, 0.65] | |
| **Injecting, ever declared** | | | | | | | | | | | | | |
| Yes | 147,341 | 704 | 47.8 | 2.17 [1.91, 2.45] | < 0.001 | 130 | 8.8 | 1.63 [1.26, 2.12] | 0.001 | 277 | 18.8 | 2.58 [2.09, 3.18] | < 0.001 |
| No | 94,298 | 476 | 50.5 | 1.98 [1.76, 2.23] | | 54 | 5.7 | 0.79 [0.58, 1.07] | | 247 | 26.2 | 3.72 [3.09, 4.49] | |
| **Undeclared** | 35,857 | 144 | 40.2 | 1.77 [1.46, 2.15] | | 30 | 8.4 | 1.51 [1.01, 2.28] | | 61 | 17.0 | 2.08 [1.54, 2.83] | |
| **Declared alcohol misuse** | | | | | | | | | | | | | |
| Yes | 45,557 | 258 | 56.6 | 1.73 [1.51, 1.99] | < 0.001 | 48 | 10.5 | 1.43 [1.04, 1.96] | 0.026 | 92 | 20.1 | 1.75 [1.39, 2.21] | < 0.001 |
| No | 332,542 | 1008 | 30.3 | 3.03 [2.72, 3.37] | | 223 | 6.7 | REF | | 381 | 11.5 | REF | |
| **Declared benzodiazepine misuse** | | | | | | | | | | | | | |
| Yes | 54,051 | 258 | 47.7 | 1.43 [1.25, 1.65] | < 0.001 | 54 | 10.0 | 1.43 [1.06, 1.94] | 0.020 | 95 | 17.6 | 1.45 [1.15, 1.82] | 0.002 |
| No | 324,049 | 1008 | 31.1 | 1.42 [1.19, 1.68] | | 217 | 6.7 | REF | | 378 | 11.7 | REF | |
| **Declared crack cocaine misuse** | | | | | | | | | | | | | |
| Yes | 136,746 | 469 | 34.3 | 0.97 [0.86, 1.09] | 0.631 | 76 | 5.6 | 0.69 [0.52, 0.90] | 0.007 | 170 | 12.4 | 0.91 [0.75, 1.11] | 0.345 |
| No | 241,353 | 797 | 33.0 | 1.42 [1.19, 1.68] | | 195 | 8.1 | REF | | 303 | 12.5 | REF | |
| **Declared cocaine/amphetamine misuse** | | | | | | | | | | | | | |
| Yes | 49,451 | 188 | 38.0 | 1.06 [0.91, 1.24] | 0.454 | 41 | 8.3 | 1.15 [0.82, 1.60] | 0.429 | 84 | 17.0 | 1.33 [1.05, 1.69] | 0.018 |
| No | 328,649 | 1078 | 32.8 | 1.04 [0.95, 1.13] | | 230 | 7.0 | REF | | 389 | 11.8 | REF | |

---

Further research

Similarly large national cohort studies of OAP clients, investigating how age-group and gender influence the opioid-specificity of client-deaths, are needed for robust generalizations outside of the UK. Within the UK, a strong public interest case can now be made for more extensive record-linkage studies to include, besides mortality and DRDs’ opioid-specificity, OAP clients’ or methadone-prescription clients’ history of hospitalizations (by which to infer co-morbidities), diagnosed carriage of blood-borne viruses (particularly the most prevalent, Hepatitis C virus), and selected co-prescribing (including for mental health conditions).

Without research, as above, into possible confounders, we can only speculate, as did Gao et al. (2016), on the underlying cause for the now confirmed steep age-gradient for methadone-specific DRDs: corrected QT prolongation, renal or liver impairment, or some other aspect of the pharmacology of methadone in older clients that makes for a longer QT prolongation, renal or liver impairment. Additionally, given the concern for sudden cardiac death linked to QTc prolongation and subsequent arrhythmias, extended monitoring in the form of Holter monitoring or loop recorders could further elucidate older clients’ risk when prescribed methadone.
Conclusion

Only formal studies will resolve what can and should be done to moderate opioid dependent clients’ increased risk of methadone-specific death as they age. Consistent findings in two major UK cohorts represent sufficient grounds for methadone prescribers, at least in the UK, to alert clients that their risk of methadone-specific death increases as they age – for reasons that we do yet fully understand. Review of older clients’ methadone dose in the light of co-morbidities and prescribed other medications may be worthwhile with consideration given, for some clients, to switching their opioid substitution formulation (McCance-Katz, 2011; Jolley et al., 2015).

Funding

Medical Research Council grant G1000021 for the NIQUAD (Nationally Integrated Quantitative Understanding of Drug-harms) Addictions Cluster. The funder had no role in the decision to publish this paper.

Contributions

SMB proposed the validation study for England to MP & TM who are its guarantors; TM holds privacy access permission for linkage of National Drug Data Warehouse (2005–2009) to Office for National Statistics mortality records, which was conducted in autumn 2011 to allow 2.5 years for the delayed registration of drugs-related deaths. SMB & JRR had instigated inquiries into Scotland’s methadone prescribing and a possible link to Scotland’s increased number of methadone-specific deaths and been co-authors of the initial study which demonstrated increased hazard for older clients; MP re-programmed previous analyses of the English cohort to focus on methadone-specific deaths; all authors contributed to the writing, referencing and review of the manuscript.

Data sharing statement

The authors are bound by the conditions imposed on their access to the Drugs Data Warehouse but can assist others in how to achieve similar access.

Transparency

The lead author (as the manuscript’s guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Ethics/privacy access approval

Data were extracted from the Drug Data Warehouse for a cohort of opioid users, aged 18 to 64 years, actively using or being treated for opioid use, in England over the period 1st April 2005 to 31st March 2009. Deaths occurring in the cohort were established by case linkage to national mortality records. Data were rendered anonymous to the research team, via irreversible encryption of identifying information, prior to their release by source organisations.

Use of mortality records was approved by the Office for National Statistics Microdata Release Panel. Use of data from the Drug Data Warehouse was authorised by those organisations providing data. The NHS Central Office for Research Ethics Committees and The University of Manchester Research Ethics Committee advised that further approval was not required for a study of this type.

Conflicts of interest

SMB served on Scotland’s National Naloxone Advisory Group and was one of three co-principal investigators for the MRC-funded N-ALIVE pilot Trial of naloxone-on-release. SMB holds GSK shares. JRR chaired Scotland’s National Forum on Drugs-related Deaths and serves on the committee which is updating UK’s opioid prescribing recommendation. SMB and JRR were co-authors of the Scottish study for which this study provides validation.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.drugpo.2018.02.005.

References

Bird, S. M., Robertson, J. R., & Strang, J. (2010). Drug-related deaths: What needs to be done. Straight Statistics http://straightstatistics.org/article/drug-related-deaths-what-now-needs-to-be-done. (Accessed 31 May 2016).

Bird, S. M., McAuley, A., Perry, S., & Hunter, C. (2016). Effectiveness of Scotland’s National Naloxone Programme for reducing opioid-related deaths: a before (2006–2010) versus after (2011–2013) comparison. Addiction, 111, 883–891. http://dx.doi.org/10.1111/add.13265.

Cornish, R., Macleod, J., Strang, J., Vickerman, P., & Hickman, M. (2010). Risk of death during and after opiate substitution treatment in primary care: Prospective observational study in UK General Practice Research Database. British Medical Journal, 341, c5475.

Cousins, G., Teljeur, C., Motterlini, N., McCowan, C., Dimitrov, B. D., & Fahey, T. (2011). Risk of drug-related mortality during periods of transition in methadone maintenance: A cohort study. Journal of Substance Abuse Treatment, 41, 252–260.

Degenhardt, L., Bucello, C., Mathers, B., Briegleb, C., Ali, H., Hickman, M., et al. (2011). Mortality among regular or dependent users of heroin and other opioids: A systematic review and meta-analysis of cohort studies. Addiction, 106(1), 32–51.

Gao, L., Dimitropoulos, P., Robertson, J. R., McGarrigle, S., Bennie, M., & Bird, S. M. (2016). Risk-factors for methadone-specific deaths in Scotland’s methadone prescription clients between 2009 and 2013. Drug and Drug Dependence, 167, 214–223.

Her Majesty’s Government. (2017). 2017 Drug Strategy. Home Office, 14 July 2017. Independent Expert Group (chair: Professor Sir John Strang). (2017). Drug misuse and dependence. UK guidelines on clinical management. Public Health England, July 2017. See Section 4.7.4.1 of https://www.gov.uk/government/publications/drug-misuse-and-dependence-uk-guidelines-on-clinical-management. (Accessed 28 July 2017).

Jolley, C. J., Bell, J., Rafferty, G. F., Moxham, J., & Strang, J. (2015). Understanding heroin overdose: A study of the acute respiratory depressant effects of injected pharmaceutical heroin. PUBLIC LIBRARY OF SCIENCE. http://dx.doi.org/10.1371/journal.pone.0140995.

Kimber, J., Copeland, L., Hickman, M., Macleod, J., McKenzie, J., De Angelis, D., et al. (2010). Survival and cessation in injecting drug users: Prospective observational study of outcome and effect of opiate substitution therapy. British Medical Journal, 341, c3172.

King, R., Bird, S. M., Overstall, A., Hay, G., & Hutchinson, S. J. (2013). Injecting drug users in Scotland, 2006: Listing, number, demography, and opiate-related death rates. Addiction Research and Theory, 21, 235–246.

King, R., Bird, S. M., Overstall, A., Hay, G., & Hutchinson, S. J. (2014). Estimating prevalence of injecting drug users and associated heroin-related death rates in England using regional data and incorporating prior information. Journal of the Royal Statistical Society Series A (Statistics in Society), 177, 1–28.

McCance-Katz, E. F. (2011). (R)-methadone versus racemic methadone: What is best for patient care? Addiction, 106, 687–688.

Merrall, E. L. C., Bird, S. M., & Hutchinson, S. J. (2012). Mortality of those who attended drug services in Scotland 1996–2010: Record linkage study. International Journal of Drug Policy, 23, 24–32.

Office for National Statistics (2017). Deaths related to drug poisoning in England and Wales: 2016 registrations. Deaths related to drug poisoning in England and Wales from 1993 onwards, by cause of death, sex, age and substances involved in the death. Office for National Statistics Statistical Bulletin See https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/bulletins/deathsrelatedtodrugpoisoninginenglandandwales/2016registration. (Accessed 7 August 2017).

Parmar, M. K. B., Strang, J., Choo, L., Meade, A. M., & Bird, S. M. (2017). Randomized
controlled pilot trial of naloxone-on-release to prevent post-prison opioid overdose deaths. *Addiction*, 112, 502–515.

Pierce, M., Bird, S. M., Hickman, M., & Millar, T. (2015). National record-linkage study of mortality for a large cohort of opiate users ascertained by drug treatment or criminal justice sources, 2005–2009. *Drug and Alcohol Dependence*, 146, 17–23.

Pierce, M., Bird, S. M., Hickman, M., Marsden, J., Dunn, G., Jones, A., et al. (2016). Impact of treatment for opioid dependence on fatal drug-related poisoning: A national cohort study in England. *Addiction*, 111, 298–308.

Romero, J., Baldinger, S. H., Goodman-Meza, D., Engstrom, K., Valencia, C. R., Golive, A., et al. (2016). Drug-induced torsades de pointes in an underserved urban population. Methadone: Is there therapeutic equipoise? *Journal of Interventional Cardiac Electrophysiology*, 45, 37–45.

Strang, J., Hall, W., Hickman, M., & Bird, S. M. (2010). Impact of supervision of methadone consumption on deaths related to methadone overdose (1993–1998): Analysis using OD4 index in England and Scotland. *British Medical Journal*, 341(641), e4851.