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Research Paper

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

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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.

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- 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; Merrall 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 co-morbidities, especially mental health conditions: antidepressants, antipsychotics, antibiotics (macrolides, quinolones, azoles), antiarrhythmics, 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

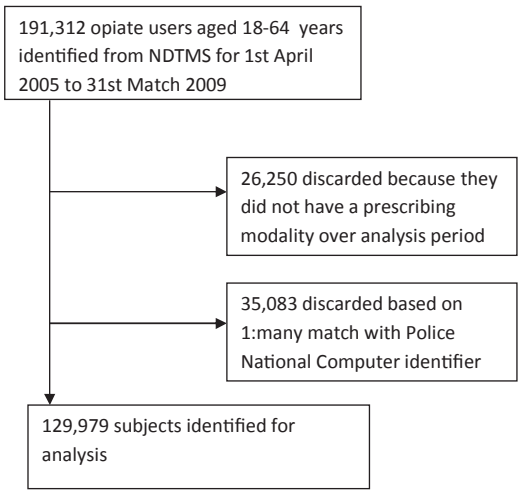

Fig. 1. Flow diagram of case-selection for the analysis cohort.