Scotland's 2009-2015 methadone-prescription cohort:

Scotland's 2009-2015 methadone-prescription cohort: quintiles for daily-dose of prescribed methadone and risk of methadone-specific death

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Running head: *Quintiles for methadone daily-dose & risks.*

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Opioid substitution therapy halves clients' drug-related death-rate.
- Yet, age-related increases drug-related and methadone-specific deaths persist.
- Opioid-cohorts lack substantial data on prescribed daily-dose of methadone.

WHAT THIS STUDY ADDS

- Validated simple rules for recovery of prescribed daily-dose of methadone.
- Baseline daily-dose of prescribed methadone available for 73% of Scotland's methadone-client cohort (2009-2015).
- Top quintile for prescribed daily-dose (> 90 mg per day) associated with increased hazard for methadone-specific death versus 50-70 mg; three times greater risk of methadone-specific death at 45+ years versus 25-34 years; females *may be* at greater risk of methadone-specific death.

Abstract

Background: As methadone-clients age, their drug-related death (DRD) risks increase, more than doubling at 45+ years for methadone-specific DRDs.

Methods: Using Community Health Index (CHI) numbers, mortality to 31 December 2015 was ascertained for 36,347 methadone-prescription-clients in Scotland during 2009-2015. Cohort-entry, quantity of prescribed methadone and daily-dose (actual or recovered by effective, simple rules) were defined by clients' first CHI-identified methadone-prescription after 30 June 2009 and used in proportional hazards analysis. As custodian of death-records, National Records of Scotland identified non-DRDs from DRDs. Methadone-specific DRD means methadone was implicated but neither heroin nor buprenorphine.

Results: The cohort's 192,928 person-years included 1857 non-DRDs; 1323 DRDs (42%), 546 being methadone-specific DRDs. Actual/recovered daily-dose was available for 26,533 (73%) clients who experienced 420 methadone-specific DRDs. Top quintile for daily-dose at first CHI-identified methadone prescription was >90mg.

Age 45+ years at cohort-entry (hazard ratio versus 25-34 years: 3.1, 95% CI: 2.4-4.2), top quintile for baseline daily-dose of prescribed methadone (versus 50-70 mg: 1.9, 1.1-3.1) and being female (1.3, 1.0-1.6) significantly increased clients' risk of methadone-specific DRD.

Conclusions: Extra care is needed when methadone daily-dose exceeds 90mg. Females' higher risk for methadone-specific DRD is new; and needs validation. Further analyses of prescribed daily-dose linked to mortality for large cohorts of methadone-clients are needed internationally; together with greater pharmacodynamic and pharmacokinetic understanding of methadone by age and gender.

Balancing age-related risks is challenging for prescribers who manage chronic opiate dependency against additional uncertainty about the nature, strength and pharmacological characteristics of drugs from illegal markets. [249 words]

Introduction

By the 1990s, UK's heroin injector epidemics of the early 1980s were being countered by opioid substitution therapy, primarily methadone, which not only reduced drug-related deaths (DRDs) [1, 2] but also blood-borne virus transmissions and criminality [3, 4]. Scotland's methadone-prescription cohort [5] includes many who are former injectors, of whom at least half will be hepatitis C virus carriers [6, 7]; most smoke; misuse of alcohol, psychiatric and physical co-morbidities are also not uncommon [8, 9].

Despite the remarkable fall in UK's DRD-rate per 1 million defined daily doses of methadone in the early 21st century [1], the present decade has seen sharply increased numbers of opioid-related deaths [10]. The UK's increase was anticipated by evidence-syntheses [11-13] and by national record-linkage studies of "virtual cohorts" of opioid-dependent clients [3, 14]. Both forewarned about demographic influences (gender; age-group) on DRD-rates, including a strong gender by age-group interaction in DRD-risk for opioid users [14, 5]. Discovering that females' advantage, in terms of lower DRD-risk, diminished with age [14] is important for risk-prediction [15] but was unrecognized in early systematic reviews [16].

We became concerned about a possible role for prescribed methadone in Scotland's rise in methadone deaths in the second decade of the 21st century [5]. Indeed, Scotland's 2009-2013 methadone-prescription cohort demonstrated that clients' risk of methadone-specific DRD increased more strikingly with age than for all DRDs [5]. Quickly, the cohort of opioid users in England's 2005-09 National Drug Treatment Management System was used to validate the Scottish results [17]. This English record-linkage cohort could adjust for a triad of major behavioural risk-factors (injector-status, misuse of alcohol, misuse of benzodiazepines) but lacked information on the prescribed quantity or daily-dose of methadone. Synthesis of the two UK studies suggested that the risk of methadone-specific DRD tripled by 45+ years of age (95% CI: 3.0 to 4.7) compared with 25-34 years [17].

Meanwhile, based on 87 DRDs in a primary care cohort, Hickman et al. [18] considered confounding between the choice of opioid substitution therapy (methadone versus buprenorphine) and the client's age-group or number of co-morbidities, both of which are potentially implicated in methadone-specific DRDs [5, 17, 19-22].

Internationally, there is a dearth of information on the daily-dose of prescribed methadone for large cohorts of opioid-dependent clients [15, 16].

Our aim is to provide alternative proportional hazards (PH) analysis for methadone-specific DRDs in Scotland's 2009-2015 methadone-prescription cohort based on:

i) clients' gender, age-group at accrual, prescription-source and baseline quintile for **quantity** (qQs) of prescribed methadone; **OR**
ii) clients' gender, age-group at accrual, prescription-source and baseline quintile for **daily-dose** (dQs) of prescribed methadone.

Methods

Definitions: drug-related deaths

We applied the UK harmonized definition of DRD [23]. National Records of Scotland [10] provided information on the opioid-specificity of Scotland's DRDs:

methadone-specific DRDs: methadone was implicated in DRD but neither heroin/morphine nor buprenorphine implicated;

heroin-specific DRDs: heroin/morphine was implicated in DRD but neither methadone nor buprenorphine implicated; and

heroin-methadone DRDs: methadone and heroin/morphine both implicated in DRD but buprenorphine was not implicated.

In appraising which drugs are implicated as causal factors in any DRD and which, although present, probably did not contribute, Scotland's pathologists are supported by having a national protocol for toxicological testing at forensic autopsies.

Scotland's Community Health Index (CHI)

Scotland's CHI is a register of all patients in National Health Service (NHS) Scotland, Scotland's publicly-funded healthcare system. From birth, patients are identified by a 10-digit CHI-number, usually the patient's date of birth (DDMMYY) followed by four digits: two randomly generated, the third identifying gender (odd for males), and the fourth a check-digit. The CHI-numbers are key to Scotland's trusted record-linkage [24], not least because deaths and hospitalizations are CHI-identified.

Scotland's methadone-prescription-client cohort for 2009-2015: data-sources and linkage

Methadone prescriptions for opioid substitution therapy fall within a specific classification category in Scotland's National Prescribing Information System [25]: most are CHI-identified, see **Figure 1**. All give quantity of methadone prescribed and number of instalments by which the prescribed quantity is issued, as both are required for the reimbursement of pharmacists. Daily-dose of prescribed methadone is not routinely available in electronic format [5, 26]. But daily-dose of prescribed methadone is available electronically for a subset of GP-prescriptions; and was extracted by Scotland's Information Services Division using Natural Language Programs applied to GPs' electronic messaging [26].

Instalment dispensing is different in Scotland: on regular GP-prescriptions, any drug is allowed and can be for any duration, although good practice suggests a limit of 28 days. In England, instalment prescriptions are for a maximum of 14 days and only allow Schedule 2 Controlled Drugs under the Misuse of Drugs Act 1971. England's 14-day limit means that quantities of prescribed methadone as large as in Scotland are unlikely.

To define Scotland's methadone-prescription-client cohort for 2009-2015, nearly 3 million methadone prescriptions during 1 July 2009 to 30 June 2015 were assessed for linkage to Scotland's mortality records to 31 December 2015. As all deaths are CHI-identified,

prescriptions' CHI-number was used for this exact linkage. The CHI-number was also used to link serial CHI-identified methadone-prescriptions for the same client.

For CHI-indexed methadone-prescriptions, we obtained: client's gender, age in completed years at 1 July of prescription-year (enabling current age-group to be used in a sensitivity analysis); prescription-date (when missing, the later re-imbursement date was used [5]); re-imbursement-date; prescription-source (GP; other-source); quantity of prescribed methadone per prescription; number of instalments per prescription; daily-dose of prescribed methadone (if extractable by Natural Language Program from GPs' electronic messaging [5, 26]); full date of death; whether underlying cause of death was non-DRD or DRD; and DRDs' opioid-specificity.

We defined Scotland's 2009-2015 methadone-prescription-client cohort as: clients with one or more CHI-identified methadone-prescription during 1 July 2009 to 30 June 2015. The client's first CHI-identified methadone-prescription during 1 July 2009 to 30 June 2015 defined cohort-entry or accrual date, baseline quantity (also daily-dose) of prescribed methadone and age-group at accrual (< 25 years, 25-34, 35-44, 45+ years).

As full date of death is potentially identifying, approval by Scotland's Public Benefit and Privacy Panel for this study required that all computations were within the Usher Institute safe-haven.

Exclusion criteria

Four types of data-checking were undertaken. First, survival time from the date of CHI-identified clients' baseline methadone-prescription was computed: negative survival times were checked for evidence of incorrect linkage. Secondly, wide outer bounds were defined for four variables, see below: CHI-identified prescriptions falling outside of any of these outer bounds were excluded as widely implausible. Third, as before [5] and on account of substitution of re-imbursement date for missing prescription-dates, we added 60 days to all CHI-identified survival intervals to ensure positivity: any residual negative times resulted in client-exclusion. Finally, a plausible upper bound of 69 years was set for age at cohort-entry for clients receiving methadone-substitution: breach of this upper bound resulted in client-exclusion.

Incorrect linkage: Computing time in days from the date of the client's baseline CHI-identified methadone-prescription to the earlier of death-date or 31 December 2015, identified 63 negative survival times. On cross-checking, Information Services Division confirmed only seven (hereafter deleted) were linked incorrectly.

Wide outer bounds: CHI-identified methadone-prescriptions in 2009-2015 were excluded if any of the following applied on a per-prescription basis:

i) quantity prescribed: < 5 mg or >12,000 mg;
ii) instalments: <1 or >84;
iii) daily-dose: <1 mg or >300 mg;
iv) age-in-prescription-year: <5 years or >79 years.

The analysis file was thereby reduced by 764 CHI-identified methadone-prescriptions (0.04%) to 1,931,326; clients by 163 to 36,444; deaths by 37, see **Figure 1**.

Ensuring positivity: As in an earlier analysis [5], because re-imbursement date was substituted for missing prescription-date, 60 days were added to all survival times. Positivity was assured for all except for five CHI-identified clients, who were excluded.

Plausible upper bound for age at cohort-entry: Ninety-two CHI-identified clients were excluded because age at cohort-entry was older than 69 years.

The two checks above together excluded 97 CHI-identified clients: 52/97 had died; 2/52 were DRDs. There remained 36,347 CHI-identified methadone-prescription clients.

Simple rules for establishing daily-dose: derivation and validation

For this paper, we devised and verified simple rules for recovery of daily-dose from quantity of prescribed methadone and number of instalments, see **APPENDIX1**.

Simple rules (hereafter, recovery-rules) were devised for establishing daily-dose from quantity of methadone prescribed and number of instalments at first CHI-identified prescription. Not every instalment number had an acceptable rule, see below. Recovery-rules were derived for CHI-identified clients who had most recently joined the cohort so that our derivation sub-cohort comprised:

a) clients from the 2009-2013 cohort [5] who received one or more CHI-identified methadone prescription **after** 30 June 2013 and were alive **after** 31 December 2013 – their accrual-date to the derivation sub-cohort was the **later** of 1 January 2014 and date of their sub-cohort-qualifying first CHI-identified methadone-prescription **after** 30 June 2013; and

b) new clients, not part of the 2009-2013 cohort [5], who received one or more CHI-identified methadone-prescriptions **after** 30 June 2013 and whose accrual-date was the date of their qualifying first CHI-identified methadone-prescription **after** 30 June 2013.

Conditional on number of instalments, a recovery-rule would be accepted if it correctly recovered at least 75% of the actual daily-doses in clients' accrual-month within the derivation sub-cohort. Our performance criteria were met when number of instalments for issuing the prescription was 4, 7, 14, 21, 28, 35, 42 or 56, see **APPENDIX1**; and verified for Scotland's 2009-2015 methadone-prescription cohort. For these listed instalment numbers, excepting 4 and 7, performance criteria were met by simply dividing quantity by number of instalments; the recovery-rules for 4 and 7 have an additional check-step. All accepted rules were then applied to recover daily-dose at cohort-entry for CHI-identified clients.

Key covariates, including quintiles for daily-dose of prescribed methadone

Key covariates were: prescription source (GP versus other-prescriber), gender (female versus male) and age-group at cohort-entry (< 25 years, 25-34, 35-44, 45+ years). In addition [5], quintile for quantity of prescribed methadone at first CHI-identified prescription (qQ) was available for all clients.

For 26,533 (73%) clients, recovery-rules allowed quintile for daily-dose of prescribed methadone at first CHI-identified prescription (dQ) to be analysed. Quintiles partition clients into fifths according to prescribed daily-dose: from the 20% receiving the lowest fifth of baseline prescribed daily-doses (dQ1) to the top 20% of prescribed daily-doses of methadone (dQ5). Using quintile-indicators allows the association between HR and increasing baseline prescribed daily-dose to be made explicit in PH regression analysis.

Statistical analysis

After documenting the impact of exclusion criteria on prescriptions, clients and deaths, we summarize the performance of recovery-rules for daily-dose for Scotland's 2009-2015 methadone-prescription cohort.

Next, for each covariate-level, we provide DRD-rates and methadone-specific DRD-rates for the cohort as a whole; and when restricted to clients with actual or recovered daily-dose at first CHI-identified prescription.

Using PH regression analysis, we assess how steeply hazard ratios (HRs) increase by age-group at accrual for methadone-specific DRDs; and how influential - based on regression chi-squares on four degrees of freedom (dfs) - are dQs versus qQs. Adjusted HRs and 95% confidence intervals are estimated simultaneously, relative to each covariate's baseline-category as shown in tables. **APPENDIX2** includes corresponding PH analyses for all DRDs which, unlike methadone-specific DRDs, require gender by age-group interaction to be taken into account. All analyses were performed using STATA v15.1; STATA's stcox was used for PH analysis.

Sensitivity analysis

APPENDIX3 includes three type of sensitivity analysis. First, rather than age-group at cohort-entry, we fitted time-updated age-group since a single transition to an older age-group could have occurred. The second analysis focuses on GP-clients solely as GP-prescriptions alone were the basis for our recovery-rules. Thirdly, the key PH analysis for methadone-specific DRDs which incorporated dose-quintiles was repeated separately: a) CHI-identified clients who entered the Scotland's 2009-2015 methadone-prescription cohort during July to December 2009 (mainly as prevalent clients; and b) CHI-identified clients who entered the cohort during 2010 and 30 June 2015 (including relatively more incident clients in their methadone titration-phase.

Results

Exploratory data analysis

Exclusions: After exclusion-steps (see **Figure 1**), the 5th and 95th percentiles for all CHI-identified methadone-prescriptions were: for quantity, 140 and 2,970 mg, mean of 1,221 mg (sd 1,025); for number of instalments, 1 and 84, mean of 13.3 instalments (sd 9.6); for actual daily-dose, 16 and 120 mg, mean of 64 mg (sd 34) – available for only 736,153 (38%) of all CHI-identified prescriptions, but for 51% of 1,429,863 CHI-identified GP-prescriptions.

Recovery rules and descriptive statistics: Eight accepted recovery rules for daily-dose at cohort-entry were generally of the form "quantity prescribed divided by D(i)" where the value for divisor D(i) depended on (i), the number of instalments (4, 7, 14, 21, 28, 35, 42 or 56), with extra conditions needed only when the number of instalments was 4 or 7 in order for at least 75% of actual daily-doses to be recovered correctly, see **APPENDIX1**: actual agreement-rate was 88% overall.

Recovered or actual daily-dose at cohort-entry was available for 26,533 (73%) of clients in Scotland's 2009-2015 cohort, including for 7,349 (58%) of the cohort's 12,743 CHI-identified clients whose prescriber was other-source, see **Table 1**. Recovered or actual daily-dose was available for 19,184 (81%) of 23,604 CHI-identified clients whose prescriber was GP.

Death-rates for Scotland's 2009-2015 methadone-prescription cohort; and when restricted to 26,533 clients with actual or recovered daily-dose of prescribed methadone.

Scotland's 2009-2015 methadone-prescription cohort comprised 36,347 CHI-identified methadone-prescription clients who experienced 1,857 non-DRDs and 1,323 DRDs, including 546 methadone-specific DRDs, in 192,928 person-years (pys) of follow-up, see **Table 2.**

Clients' non-DRD rate was 9.6 per 1000 pys versus their DRD-rate of 6.9 per 1000 pys, both precisely-estimated. The 65% of clients with a GP-prescriber had lower DRD-rate (and lower methadone-specific DRD-rate) than clients whose prescriber was other-source. Two-thirds of clients were male, for whom methadone-specific DRD-rate was lower at 2.6 per 1000 pys (95% CI: 2.4-2.9) than for females (3.2, 95% CI: 2.8-3.7).

Both DRD-rate and methadone-specific DRD rate increased with age-group at cohort-entry, the latter more steeply. The modal age-group at accrual to Scotland's 2009-2015 methadone-prescription cohort was 25-34 years of age (44% of clients) with only 8% of clients aged 15-24 years. Methadone-specific DRD-rate was significantly higher for clients in the top quintile for prescribed quantity at accrual to the cohort (qQ5: 4.3 per 1000 pys, 95% CI: 3.7-5.0) than for clients in the middle quintile (qQ3: 2.1 per 1000pys, 95% CI: 1.7-2.6).

Table 3 presents corresponding information for the 26,533 clients with actual or recovered daily-dose of prescribed methadone at first CHI-identified prescription, 72% of whom had a GP-prescriber. Their DRDs numbered 995, including 420 methadone-specific DRDs. Methadone-specific DRD-rate was significantly higher for clients in the top quintile for prescribed daily-dose at accrual (dQ5 [> 90 mg]: 5.0 per 1000 pys, 95% CI: 4.2-6.0) than for clients in the middle quintile (dQ3 [50-70 mg]: 2.7 per 1000 pys, 95% CI: 2.2-3.3).

Adjusted hazard-ratios for methadone-specific DRDs in Scotland's 2009-2015 methadone-prescription cohort.

Baseline quintile for prescribed quantity, Table 4: For methadone-specific DRDs, interaction between gender and age-group is unnecessary (chi-square on 3 degrees of freedom of 4.00, p ~ 0.026, see **APPENDIX2**). Females have higher HR (1.4) than males; HRs increase very steeply with age-group at cohort-entry, being 3-fold higher for clients 45+ years and 2-fold greater for clients aged 35-44 years than if 25-34 years old at cohort-entry. Only the top quintile for quantity of prescribed methadone was associated with a significantly increased HR compared to qQ3. Clients whose prescription-source was non-GP had significantly higher methadone-specific risk (HR, 1.36); likewise, DRD-risk (see **APPENDIX2:** HR, 1.31).

Baseline quintile for recovered or actual daily-dose, Table 5: For methadone-specific DRDs, females are disadvantaged (HR 1.3, 95% CI: 1.0-1.6) and the steepness of increase in HRs, both age-related and by quintile for baseline daily-dose, is much greater than for all DRDs (see **APPENDIX2**). By age-group at cohort-entry, HR was 3-fold higher (95% CI: 2.4 to 4.2) at 45+ years than at 25-34 years. For dQ5, HR was also 3-fold higher (95% CI: 2.2 to 4.5) than for dQ1 and significantly greater than for dQ3 (HR = 3.15/1.68 or 1.88; 95% CI: 1.13 to 3.12), itself significantly greater than dQ1. Finally, higher HR for methadone-specific DRD was again associated with other-source prescribers (HR, 1.3, 95% CI: 1.1-1.6).

Notice that for 420 clients aged 45+ years at cohort-entry who received baseline methadone daily-dose greater than 90 mg, methadone-specific DRD-rate was 6.5 per 1000 pys (95% CI: 3.9 to 10.7, based on 15 methadone-specific DRDs in 2,138 pys,) versus 1.6 (95% CI: 1.1 to 2.4, based on 24 methadone specific DRDs in 14,869 pys) for 2,627 clients in dQ3 and aged 25-34 years at cohort-entry.

Sensitivity analyses: See **APPENDIX3** for three sensitivity analyses. The first relates to current age-group rather than age-group at cohort-entry (**Table A4**). Since clients' age-group changes at most once during follow-up, age-effects sharpened only slightly with current age-group as alternative to age-group at accrual. The second focuses on GP-clients only, as GPs' prescriptions were the basis for our recovery-rules (**Table A5**), but still endorses **Table 5**. Thirdly, **APPENDIX3** re-estimates **Table 5** for the sub-cohort of mainly prevalent CHI-identified clients whose cohort-entry was in July to December 2009 (**Table A6)** versus later-recruited CHI-identified clients (**Table A7**). The mainly prevalent sub-cohort is the larger; clients are older at cohort-entry, only 19% had a non-GP prescriber and only 5% had baseline daily-dose in dQ1. Nonetheless, inferences about age-group and dQs are broadly similar for the two sub-cohorts. We note, however, that the mainly prevalent clients' hazard of methadone-specific DRD did not differ by prescription-source.

Discussion

Summary of main findings

Daily-dose at first CHI-identified methadone prescription was analysed for 73% of clients in Scotland's 2009-2015 methadone-prescription cohort. Daily-doses greater than 50 mg up to 70 mg comprised the mid-quintile (dQ3). Top quintile (dQ5) was daily-dose >90 mg, within which mean daily-dose (sd) was 117 mg (sd 25).

For methadone-specific DRDs, HR increased steeply for the two older age-groups and steadily with quintile for daily-dose through to 3.1 (95% CI: 2.2 to 4.5) for dQ5; and females were at greater risk, a new finding.

For methadone-specific DRDs and for all DRDs, we found an increased hazard (HR 1.3) associated non-GP prescribers: clients' physical and psychiatric comorbidities may be less well-known by other-prescribers than by GPs.

For context, non-DRDs outnumbered DRDs by 3:1 for methadone-prescription clients aged 45 years and over.

Key considerations

Notwithstanding the substantial reduction in harms (overdose deaths, criminality and blood-borne virus risks) that opioid substitution therapy has delivered for younger heroin users, the risk of methadone-specific DRD increases both as clients age into their 40s and 50s; and steadily with baseline quintile for daily-dose of prescribed methadone.

Guidelines for methadone-clients recommend a daily-dose of 60-120 mg [27]. Adherence to prior guidance was checked by prescribing surveys [28-31] or evidence-synthesis [1]. But Scotland's 2009-2015 methadone-prescription cohort is the first major cohort internationally to have analysed the joint effects of gender, age-group and baseline daily-dose of prescribed methadone on both methadone-specific DRDs and all DRDs.

In some individuals, females especially [32], methadone (unlike buprenorphine [18]) is associated with prolongation of the QTc interval leading to the development of Torsades de Pointes and cardiac arrest [33]. *Undiagnosed QTc* prolongation may manifest as methadone-specific DRDs.

Periodic electrocardiograms are recommended for clients receiving more than 100 mg of methadone daily [33], but not achieved in practice. Other risk-factors for QTc prolongation include co-morbidities such as circulatory or liver disease; co-prescribing for mental or physical ill-health [34]; use of both methadone and cocaine; and being female [32, 35]. Could the latter partly explain our novel finding that females are at higher risk of methadone-specific DRD [35-38]?

Confounding between methadone-specific DRD-risk and the client's daily-dose of prescribed methadone (dQ) cannot be excluded. However, of Hill's nine criteria for ascribing cause [39],

dQs meet at least six: strength of association, specificity (versus all DRDs), temporality, biological gradient, plausibility, and coherence.

Balancing of prescribing risks is challenging in clinical practice, never more so than when managing chronic opiate dependency. Risks include [27]: the toxicity of prescribed opiates; co-existing respiratory, cardiovascular and metabolic hazards, for example from compromised liver capacity; the potential dangers of cumulative doses of multiple drugs beyond an individual patient's current tolerance; compounded by ignorance of the nature, strength and pharmacological characteristics of drugs that clients may access on the illegal market. The latter vary notoriously in time and place.

The above considerations produce an environment of high risk for overdose toxicity and sudden death. Information, as in this paper, which might mitigate some of these risks is, therefore, important.

We have raised a concern about higher DRD-risks for methadone-clients of non-GP prescribers: in particular, for methadone-prescription clients whose cohort entry-date was during 2010-2015, a period when non-medical prescribing in the management of substance misuse had expanded in Scotland, as elsewhere [40]. Scotland's GPs have not been reluctant to manage methadone-prescriptions for clients with major co-morbidities as around 80% of CHI-identified clients whose cohort-entry was July-December 2009 had GP-prescribers. In terms of risk-mitigation, it might be helpful for GP Summary Care Records to be routinely available to specialist service prescribers so that they are aware of ageing clients' co-morbidities.

In a changing landscape of funding, commissioning of services and basic training of prescribers, both Scotland and the rest of the UK are moving towards a wider range of prescribers who include pharmacists and specialist nurses. Our paper draws attention to the complexity of need that ageing methadone-clients have for interventions from a variety of chronic disease specialists (respiratory, cardiovascular and gastrointestinal) beyond their immediate drug problems. Primary care, in its widest sense, aspires to be the focus for multidisciplinary care.

Strengths and limitations of this study

First, Scotland has a national protocol for toxicology at forensic autopsies which underwrites the opioid-specificity of Scotland's DRDs. Second, and unparalleled for a national cohort, we could analyse quintiles for daily-dose of prescribed methadone at cohort-entry for over 26,500 methadone-clients in 2009-2015 who experienced 995 DRDs, 420 of them methadone-specific DRDs. Thirdly, representativeness in terms of daily-dose at cohort-entry is supported because actual or recovered daily-dose was available for 73% of all clients in Scotland's CHI-identified methadone-client cohort; and for 81% of GP-clients.

Fourth, to minimize ascertainment bias, we considered only the baseline (not time-varying) quantity of methadone prescribed at first CHI-identified prescription. This first CHI-identified prescription defined the client's entry to Scotland's methadone-client cohort (2009-2015)

but was not typically the client's first methadone prescription, especially if cohort-entry was in 2009. Accrual-date was July-December 2009 for 57% of clients, indicating that clients were mainly prevalent at cohort-entry, see also Gao et al. [5]. Clients whose first CHI-identified methadone prescription occurred during 2010 to June 2015 include incident clients whose baseline daily-dose of methadone was captured during the clients' titration phase.

Fifth, our results on quantity and daily-dose were robust when restricted to GP-clients only or based on current age-group versus age-group at cohort-entry or when the mainly prevalent sub-cohort of clients whose cohort-entry was in July to December 2009 was analysed separately.

There are several limitations. First, only 66% of all Scotland's methadone-prescriptions in 2009-2015 were CHI-identified. However, as a best estimate, our 36,347 CHI-identified methadone-clients represent 80% (plausible range: 70% to 90%) of Scotland's methadone-clients during 2009-2015, because a substantial proportion of methadone-prescriptions which lack a CHI-number may pertain to already CHI-identified clients. Hence, we do not use time-updated quantity prescribed or daily-dose because we cannot be certain that the most recent CHI-identified methadone-prescription is the client's most recent methadone-prescription.

In deriving simple rules for recovery of daily-dose, a limitation was that actual daily-doses were available electronically from GP-prescriptions only but recovery-rules were applied to other-source prescriptions on the reasonable assumption that the same relationships hold. As a check, PH analyses using quintiles for daily-dose were repeated for GP-prescribed clients only: and inferences were essentially unaltered.

Record-linkage studies have limited scope for resolving data-queries. We took a harder line than previously on exclusion criteria, respectively for prescriptions and clients.

The need to substitute the later re-imbursement date for missing 1st prescription-date was a minor issue. More importantly, we did not know, and so could not analyse, when clients exited from methadone-therapy as the date of their last CHI-identified methadone-prescription does not exclude later non-CHI-identified prescriptions. Hence, once included in the cohort, clients have remained in follow-up.

Confounding between DRD-risk and the client's daily-dose quintile cannot be ruled out [18]. Age over 45 years and prescribed daily-dose greater than 90 mg may be markers for harder-to-support clients whose opioid dependency is chronic, who have physical co-morbidities, notably circulatory and digestive system diseases, or co-prescriptions for mental or physical ill-health [8].

Finally, we did not request that methadone clients' co-prescriptions [34] for benzodiazepines, antiviral medications, mirtazapine, amitriptyline, sertraline or macrolide antibiotics (to name but a few) be linked-in because the added time and complexity would not have been warranted given that illicit supplies would have remained unaccounted for: and constitute most of the benzodiazepines present at Scotland's DRDs [8].

Conclusions

Scotland's 2009-2015 methadone-prescription cohort helps to explain why UK official statistics on DRDs and opioid-specific deaths in the second decade of 21st show stark increases by age-group, and disproportionately so for females [10]. Methadone-prescription clients, including CHI-unidentified, during July 2009 to June 2015 accounted for around 70% (546/0.80 coverage] of Scotland's 983 methadone-specific DRDs in July 2009 to 31 December 2015.

Our analyses shed an uncompromising light on the wave of age-related, opioid-specific DRDs that overwhelms survivors from the UK's heroin injector epidemics of the early 1980s. Clinicians have a difficult balance to strike. Unlike record-linkage studies, official statistics do not chart clients' non-DRDs, which predominate over DRDs by at least 3: 1 as clients age beyond 45 years. And sustained methadone maintenance, as recommended [27], has halved the DRD-rate that clients would otherwise have experienced at an age when DRDs did predominate.

Urgently, interventions are needed to de-escalate ageing methadone-clients' risk not only of methadone-specific DRD but also of their major causes of non-DRDs [19]. Practitioners must balance: moderation of clients' daily-dose of methadone, ideally to below 90 mg if clients are willing; review of circulatory or digestive co-morbidities which respectively risk sudden death masquerading as methadone-specific DRD or prolongation of methadone's half-life; support for smoking cessation to manage better the client's respiratory and circulatory diseases; hepatitis C virus clearance by directly acting antiviral therapy; and review of medications prescribed for psychiatric and physical co-morbidities for possible interactions with methadone [34].

Methadone exhibits large inter-individual variation in response, a narrow therapeutic index and interacts with a range of other drugs commonly prescribed for ageing methadone-prescription clients' co-morbidities. Too little is known about the age-related or gendered pharmacogenomics, pharmacokinetics and pharmacodynamics of methadone [22, 32, 41]. [4,391 words]

Legend for Figure 1 Exploratory data analysis: from Scotland's over 2.9 million methadone-prescriptions during 1 July 2009 to 30 June 2015 to 36,347 CHI-identified methadone-prescription clients followed-up to 31 December 2015.

Conflicts of Interest: *LG has no conflicts; JRR chaired Scotland's National Forum on Drugs-Related Deaths and served on UK's Independent Expert Working Group on Drug Misuse and Dependence; SMB holds GSK shares and served on Scotland's National Naloxone Advisory Group.*

Data Sharing: Data were made available for analysis after our application to Scotland's Electronic Data Research and Innovation Service (eDRIS) was approved by Scotland's Public Benefit and Privacy Panel (PBPP). The data can be accessed by other research-teams who submit a successful PBPP-application via eDRIS but are not available directly from the authors.

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Table 1: Descriptive statistics for Scotland's 2009-2015 CHI-identified methadone-prescription cohort

Descriptor	**2009-2015 CHI-identified methadone-prescription cohort**	
	All clients	With actual or recovered daily-dose at first CHI-identified prescription
Clients	36,347	26, 533
Person-years (pys)	192,928 pys	144,697 pys
Deaths	3,180	2,342
DRDs (%)	1,323 (42%)	995 (42%)
Methadone-specific DRDs (% of all DRDs)	546 (41%)	420 (42%)
Heroin-specific DRDs (% of all DRDs)	320 (24%)	241 (24%)
Heroin + methadone DRDs (% of all DRDs)	309 (23%)	219 (22%)
Gender		
Females (%)	12,096 (33%)	8,744 (33%)
Males (%)	24,251 (67%)	17,789 (67%)
Prescription source		
GP-prescriber	23,604 (65%)	19,184 (72%)
Other-source prescriber	12,743 (35%)	7,349 (28%)
Means (sd)		
Age at accrual	34.8 years (7.9)	34.9 years (7.8)
1st actual or recovered daily-dose at accrual	61.7 mg (34.2) 11,055 clients with actual daily-dose	62.8 mg (33.2) 26,533 clients with actual or recovered daily-dose
Quantity methadone at 1st CHI-identified script in accrual month	1,181 mg (1,116)	1,260 mg (1,112)
Client's number of CHI-identified prescriptions with actual or recovered daily-dose in accrual month		
1		17,349 (65%)
2		6,393 (24%)
3		1,926 (7%)
4		601 (2%)
5 or more		264 (1%)
Clients' accrual era		
July-December 2009	20,728	16,350
2010	6,489	4,428
2011	2,993	1,973
2012	1,938	1,274
January-June 2013	813	517
July-December 2013	985	577
2014	1,661	979
January-June 2015	740	435

Table 2: Death-rates (95% confidence interval) for 1000 person-years for all 36,347 clients in Scotland's 2009-2015 CHI-identified methadone-prescription cohort

All CHI-identified methadone-prescription clients								
Covariate	Clients (%)	Total CHI-identified prescriptions	Person-years	Non-DRDs	DRDs	**Methadone-specific DRDs [M]** (%)	Heroin-specific DRDs [H]	M+H DRDs
Scotland-wide	36,347	1,931,062	192,928	1,857	1,323	**546**	320	309
Death-rates (95% confidence interval)				9.6 (9.2-10.1)	6.9 (6.5-7.2)	**2.8** (2.6-3.1)	1.7 (1.5-1.9)	1.6 (1.4-1.8)
Prescription-source								
GP	23,604 (65%)	1,419,112	130,856	1,351 (73%)	846 (64%)	**347** (64%)	226	165
Death-rates (95% confidence interval)				10.3 (9.8-10.9)	6.5 (6.0-6.9)	**2.7** (2.4-2.9)		
Other - source	12,743 (35%)	511,950	62,072	506 (27%)	477 (36%)	**199** (36%)	94	144
Death-rates (95% confidence interval)				8.2 (7.5- 8.9)	7.7 (7.0-8.4)	**3.2** (2.8-3.7)		
Gender								
Male	24,251 (67%)	1,253,996	128,042	1,315 (71%)	908 (69%)	**339** (62%)	252	218
Death-rates (95% confidence interval)				10.3 (9.7-10.8)	7.1 (6.6-7.6)	**2.6** (2.4-2.9)		
Female	12,096 (33%)	677,066	64,886	542 (29%)	415 (31%)	**207** (38%)	68	91
Death-rates (95% confidence interval)				8.4 (7.7- 9.1)	6.4 (5.8-7.0)	**3.2** (2.8-3.7)		
Age-group at baseline, that is: at accrual								
15-24 years	2,965 (8%)	131,287	14,941	50 (3%)	64 (5%)	**20** (4%)	23	15
Death-rates (95% confidence interval)				3.3 (2.5- 4.4)	4.3 (3.4- 5.5)	**1.3** (0.9-2.1)		
25-34 years	15,957 (44%)	862,064	86,825	408 (21%)	504 (38%)	**163** (30%)	154	137
Death-rates (95% confidence interval)				4.7 (4.3- 5.2)	5.8 (5.3- 6.3)	**1.9** (1.6-2.2)		
35-44 years	13,416 (37%)	751,673	72,207	803 (42%)	567 (43%)	**264** (48%)	116	118
Death-rates (95% confidence interval)				11.1 (10.4-11.9)	7.9 (7.2- 8.5)	**3.7** (3.2-4.1)		
45 + Years	4,009 (11%)	186,038	18,956	596 (34%)	188 (14%)	**99** (18%)	27	39
Death-rates (95% confidence interval)				31.4 (29.0-34.1)	9.9 (8.6-11.4)	**5.2** (4.3-6.4)		
Quintiles for baseline quantity of prescribed methadone defined by 1st CHI-identified prescription[1]								
qQ1: 5 to 270 mg	7,282 (20%)	321,751	32,396	368 (20%)	224 (17%)	**77** (14%)	75	41
Death-rates (95% confidence interval)				11.4 (10.3-12.6)	6.9 (6.1-7.9)	**2.4** (1.9-3.0)		

qQ2: 271 to 645 mg	7,259 (20%)	378,255	37,117	384 (21%)	271 (20%)	**92** (17%)	77	68
Death-rates (95% confidence interval)				10.3 (9.4-11.4)	7.3 (6.5-8.2)	**2.5** (2.0-3.0)		
qQ3: 646 to 1120 mg	7,298 (20%)	438,174	40,542	351 (19%)	250 (19%)	**85** (16%)	71	66
Death-rates (95% confidence interval)				8.7 (7.8- 9.6)	6.2 (5.4-7.0)	**2.1** (1.7-2.6)		
qQ4: 1121 to 1960 mg	7,915 (22%)	450,504	44,478	413 (22%)	288 (22%)	**128** (23%)	62	69
Death-rates (95% confidence interval)				9.3 (8.4-10.2)	6.5 (5.8-7.3)	**2.9** (2.4-3.4)		
qQ5: > 1960 mg	6,593 (18%)	351,378	38,395	341 (18%)	290 (22%)	**164** (30%)	35	65
Death-rates (95% confidence interval)				8.9 (8.0- 9.9)	7.6 (6.7-8.5)	**4.3** (3.7-5.0)		

[1]***Quintiles for baseline quantity of prescribed methadone defined by 1st CHI-identified prescription, are as follows*** qQ1: 5 to 270 mg; qQ2: 271 to 645 mg; qQ3: 646 to 1120 mg; qQ4: 1121 to 1960 mg; qQ5: > 1960 mg

Table 3: Death-rates (95% confidence interval) for 1000 person-years for 26,533 clients in Scotland's 2009-2015 CHI-identified methadone-prescription cohort with actual or recovered daily-dose at first CHI-identified prescription

Clients with actual or recovered daily-dose at first CHI-identified prescription								
Covariate	Clients (%)	Total CHI-identified prescriptions	Person-years	Non-DRDs (%)	DRDs (%)	**Methadone-specific DRD [M]** (%)	Heroin-specific DRD [H]	M+H DRDs
Scotland-wide	26,533	1,510,417	144,697	1,347	995	**420**	241	219
Death-rates (95% confidence interval)				9.3 (8.8-9.8)	6.9 (6.5-7.3)	**2.9** (2.6-3.2)		
Prescription-source								
GP	19,184 (72%)	1,178,699	107,248	1,030 (76%)	706 (71%)	**293** (70%)	184	136
Death-rates (95% confidence interval)				9.6 (9.0-10.2)	6.6 (6.1-7.1)	**2.7** (2.4-3.1)		
Other - source	7,349 (28%)	331,718	37,449	317 (24%)	289 (29%)	**127** (30%)	57	83
Death-rates (95% confidence interval)				8.5 (7.6-9.5)	7.7 (6.9-8.7)	**3.4** (2.9-4.0)		
Gender								
Male	17,789 (67%)	985,116	96,377	970 (72%)	696 (70%)	**269** (64%)	196	156
Death-rates (95% confidence interval)				10.1 (9.5-10.7)	7.2 (6.7-7.8)	**2.8** (2.5-3.2)		
Female	8,744 (33%)	525,301	48,320	377 (28%)	299 (30%)	**151** (36%)	45	63
Death-rates (95% confidence interval)				7.8 (7.0-8.6)	6.2 (5.5-6.9)	**3.1** (2.7-3.7)		
Age-group at baseline, that is: at accrual								
15-24 years	1,991 (8%)	96,353	10,355	36 (3%)	40 (4%)	**13** (3%)	14	8
Death-rates (95% confidence interval)				3.5 (2.5- 4.8)	3.9 (2.8-5.3)	**1.3** (0.7-2.2)		
25-34 years	11,567 (44%)	666,980	64,492	299 (22%)	370 (37%)	**123** (29%)	115	93
Death-rates (95% confidence interval)				4.6 (4.1- 5.2)	5.7 (5.2-6.4)	**1.9** (1.6-2.3)		
35-44 years	10,054 (38%)	599,478	55,553	594 (44%)	435 (44%)	**206** (49%)	91	88
Death-rates (95% confidence interval)				10.7 (9.9-11.6)	7.8 (7.1- 8.6)	**3.7** (3.2-4.3)		
45 + Years	2,921 (11%)	147,606	14,297	418 (31%)	150 (15%)	**78** (19%)	21	30
Death-rates (95% confidence interval)				29.2 (26.6-32.2)	10.4 (8.9-12.3)	**5.4** (4.4-6.8)		
Quintiles (qQ) for baseline quantity of prescribed methadone defined by 1st CHI-identified prescription[1]								
qQ1: 5 to 336 mg	5,318 (20%)	251,575	25,025	274 (20%)	179 (18%)	**57** (14%)	64	29
Death-rates (95% confidence interval)				11.0	7.2	**2.3**		

				(9.9-12.3)	(6.2-8.3)	(1.8-3.0)		
qQ2: 337 to 765 mg	5,296 (20%)	308,169	28,345	268 (20%)	207 (21%)	**66** (16%)	65	53
Death-rates (95% confidence interval)				9.5 (8.4-10.7)	7.3 (6.4-8.4)	**2.3** (1.8-3.0)		
qQ3: 766 to 1260 mg	5,714 (22%)	368,734	32,505	291 (22%)	191 (19%)	**82** (20%)	48	38
Death-rates (95% confidence interval)				9.0 (8.0-10.0)	5.9 (5.1-6.8)	**2.5** (2.0-3.1)		
qQ4: 1261 to 1960 mg	4,979 (19%)	290,517	28,258	250 (19%)	182 (18%)	**80** (19%)	35	50
Death-rates (95% confidence interval)				8.9 (7.8-10.0)	6.4 (5.6-7.4)	**2.8** (2.3-3.5)		
Q5: > 1960 mg	5,226 (20%)	291,422	30,564	264 (20%)	236 (24%)	**135** (32%)	29	49
Death-rates (95% confidence interval)				8.6 (7.7-9.7)	7.7 (6.8-8.8)	**4.4** (3.7-5.2)		
Quintiles (dQ) for baseline daily-dose of prescribed methadone defined by 1st CHI-identified prescription[2]								
dQ1: [1 - 34.5] mg	5,307 (20%)	244,273	26,499	327 (24%)	152 (15%)	**41** (10%)	54	29
Death-rates (95% confidence interval)				12.3 (11.1-13.8)	5.7 (4.9-6.7)	**1.6** (1.1-2.1)		
dQ2: (34.5-50]mg	6,287 (24%)	336,090	32,918	294 (22%)	212 (22%)	**72** (17%)	62	45
Death-rates (95% confidence interval)				8.3 (7.4-9.4)	6.3 (5.5-7.3)	**2.2** (1.7-2.8)		
dQ3: (50 - 70] mg	5,892 (22%)	348,984	32,859	274 (20%)	208 (21%)	**87** (21%)	52	55
Death-rates (95% confidence interval)				8.3 (7.4-9.4)	6.3 (5.5-7.3)	**2.7** (2.2-3.3)		
dQ4: (70 - 90] mg	4,645 (18%)	288,961	26,658	234 (17%)	199 (20%)	**91** (22%)	44	46
Death-rates (95% confidence interval)				8.8 (7.7-10.0)	7.5 (6.5-8.6)	**3.4** (2.8-4.2)		
dQ5: > 90 mg	4,402 (17%)	292,109	25,763	218 (16%)	224 (23%)	**129** (31%)	29	44
Death-rates (95% confidence interval)				8.5 (7.4-9.7)	8.7 (7.6-9.9)	**5.0** (4.2-6.0)		

[1]Quintiles (qQ) for baseline quantity of prescribed methadone defined by 1st CHI-identified prescription are as follows qQ1: 5 to 336 mg; qQ2: 337 to 765 mg; qQ3: 766 to 1260 mg; qQ4: 1261 to 1960 mg; Q5: > 1960 mg

[2]Quintiles (dQ) for baseline daily-dose of prescribed methadone defined by 1st CHI-identified prescription are as follows dQ1: [1 - 34.5] mg; dQ2: (34.5-50] mg; dQ3: (50 - 70] mg; dQ4: (70 - 90] mg; dQ5: > 90 mg

Table 4: Proportional hazards regression for methadone-specific DRDs for 36,347 clients with 192,928 person-years of follow-up in Scotland's 2009-2015 CHI-identified methadone-prescription cohort, incorporating quintiles for quantity of methadone prescribed at first CHI-identified methadone-prescription (qQ).

Quintiles for baseline quantity of prescribed methadone at 1st CHI-identified prescription (qQ) qQ regression chi-square of **33.40** on 4 degrees of freedom; p < 0.00001		
Events	**546 Methadone-specific DRDs**	
Covariates	**Hazard Ratio (HR)**	95% Confidence Interval for HR; p-value versus baseline
Prescription-source (baseline: GP-prescriber)		
Other-source	**1.36**	1.14-1.62; p ~ 0.001
Gender (baseline: male)		
Female	**1.37**	1.15-1.63; p < 0.001
Age-group at accrual (baseline: 25-34 years)		
< 25 years	**0.67**	0.42-1.07
25-34	**1.00**	**Baseline**
35-44	**2.02**	1.66-2.46; p < 0.001
45+ years	**2.94**	2.29-3.78; p < 0.001
Quintiles for prescribed quantity at accrual (qQ1 as baseline)		
qQ1: 5 - 270 mg	**1.00**	**Baseline**
qQ2: 271 - 645 mg	**0.98**	0.72-1.33
qQ3 646 - 1120 mg	**0.79**	0.58-1.07
qQ4: 1121 - 1960 mg	**1.08**	0.81-1.44
qQ5: > 1960 mg	**1.61**	1.22-2.11; p ~ 0.001

Table 5: Proportional hazards regression for methadone-specific DRDs for 26,533 clients Scotland's 2009-2015 CHI-identified methadone-prescription cohort with actual or recovered daily-dose of methadone at first CHI-identified methadone-prescription and 144,697 person-years of follow-up.

Quintiles for actual or recovered daily-dose of methadone at 1st CHI-identified prescription (dQ) dQ regression chi-square of ***58.99*** on 4 degrees of freedom; p < 0.00001		
Events	**420 Methadone-specific DRDs**	
Covariates	Hazard Ratio (HR)	95% confidence interval for HR; p-value versus baseline
Prescription-source (baseline: GP-prescriber)		
Other-source	**1.32**	1.07-1.63; p ~ 0.009
Gender (baseline: male)		
Female	**1.29**	1.05-1.58; p ~ 0.013
Age-group at accrual (baseline: 25-34 years)		
< 25 years	**0.67**	0.38-1.19
25-34	**1.00**	**Baseline**
35-44	**2.00**	1.60-2.50; p < 0.001
45+ years	**3.15**	2.37-4.19; p < 0.001
Quintiles for prescribed quantity at accrual (qQ1 as baseline)		
dQ1: [1 - 34.5] mg	**1.00**	**Baseline**
dQ2: (34.5 - 50] mg	**1.39**	0.95-2.04
dQ3 (50 - 70] mg	**1.68**	1.15-2.43; p ~ 0.007
dQ4: (70 - 90] mg	**2.16**	1.49-3.13; p < 0.001
dQ5: > 90 mg	**3.15**	2.21-4.48; p < 0.001

APPENDICES

Appendix1: Rules for recovery of daily-dose

Accepted rules for recovery of daily-dose: The performance of recovery rules, see **Table A1**, was tested in alternative settings:

i) Scotland's 2013-15 derivation sub-cohort, as defined in **Methods**: all CHI-identified prescriptions with daily-dose in clients' accrual month.
ii) Scotland's 2009-2015 methadone-prescription-client cohort: all CHI-identified prescriptions with daily-dose in clients' cohort-entry month.

As shown in **Table A1**, recovery rules were generally of the form "quantity divided by D(i)" where the value, D (i), depended on the number (i) of instalments, with extra conditions needed only when the number of instalments was 4 or 7.

To be accepted, a recovery-rule for i instalments had to match 75% of actual daily-doses issued in i instalments in the accrual month for clients in the derivation sub-cohort. The accepted rules recovered 90% of 7,964 relevant daily-doses for clients in the derivation sub-cohort; and 88% of 8,389 relevant daily-doses in the cohort-entry month for Scotland's 2009-2015 methadone-prescription-client cohort. Recovery-rate dropped below 75% in Scotland's 2009-2015 cohort only twice: for 4 instalments (71%) and 35 instalments (67%).

Table A1: Performance of accepted recovery rules for daily-dose

Number of instalments with acceptable recovery-rule	Accepted recovery rule for daily-dose	Performance of per-instalment recovery rule	Scotland's 2009-2015 methadone-prescription cohort: accrual month	2013-2015 derivation sub-cohort: accrual month
4	If number of instalments is the same for every prescription in client's accrual month: divide quantity by 28. Otherwise divide quantity by 4 unless answer exceeds 200 mg, in which case divide by 28	% correct versus actual daily-dose	71% (1,251/1,765)	76% (1,374/1,805)
		Increase in daily-dose by applying rule	Increased from 1,765 to 5,276	Increased from 1,805 to 4,413
		Number other-source prescriptions with daily-dose by applying rule	1,305	1,498
7	Divide quantity by 7 unless answer	% correct versus actual daily-dose	90% (1,818/2,020)	92% (1,289/1,402)

	exceeds 200 mg, in which case divide by 49, that is: 7 * 7.	Increase in daily-dose by applying rule	Increased from 2,020 to 7,550	Increased from 1,402 to 4,346
		Number other-source prescriptions with daily-dose by applying rule	1274	828
14	Divide quantity by 14	% correct versus actual daily-dose	94% (1,950/2,081)	95% (1,710/1,802)
		Increase in daily-dose by applying rule	Increased from 2,081 to 9,416	Increased from 1,802 to 8,229
		Number other-source prescriptions with daily-dose by applying rule	3,979	3,921
21	Divide quantity by 21	% correct versus actual daily-dose	86% (331/ 386)	90% (353/ 391)
		Increase in daily-dose by applying rule	Increased from 386 to 1,231	Increased from 391 to 1,072
		Number other-source prescriptions with daily-dose by applying rule	135	132
28	Divide quantity by 28	% correct versus actual daily-dose	96% (1,863/1,950)	97% (2,289/2,365)
		Increase in daily-dose by applying rule	Increased from 1,950 to 6,461	Increased from 2,365 to 6,924
		Number other-source prescriptions with daily-dose by applying rule	2730	2893
35	Divide quantity by 35	% correct versus actual daily-dose	67% (24/ 36)	78% (21/ 27)
		Increase in daily-dose by applying rule	Increased from 36 to 65	Increased from 27 to 53
		Number other-source prescriptions with daily-dose by applying rule	5	0
42	Divide quantity by 42	% correct versus actual daily-dose	78% (59/ 76)	87% (72/ 83)
		Increase in daily-dose by applying rule	Increased from 76 to 118	Increased from 83 to 91

		Number other-source prescriptions with daily-dose by applying rule	5	0
56	Divide quantity by 56	% correct versus actual daily-dose	96% (72/ 75)	98% (87/ 89)
		Increase in daily-dose by applying rule	Increased from 75 to 112	Increased from 89 to 109
		Number other-source prescriptions with daily-dose by applying rule	11	7
By applying the above eight accepted rules for recovery of daily-dose when number of instalments is: 4, 7, 14, 21, 28, 35, 42 or 56		% correct versus actual daily-dose	88% (7,368/8,389)	90% (7,195/7,964)
	Increase in daily-dose by applying rule		Increased from 8,389 to 30,229	Increased from 7,964 to 25,237
	Number other-source prescriptions with daily-dose by applying rule		9,444	9,279

Appendix2: Proportional hazards (PH) analysis for all DRDs

Baseline quintile for prescribed quantity: For all DRDs, **Table A2** shows that the interaction between gender and age-group at accrual is highly statistically significant (p ~ 0.0026) and signals that female clients' reduced DRD-hazard (overall HR, 0.82) is reversed for older clients. Male clients' DRD-risk increases with age, being significantly greater for males aged 45+ years at accrual (HR, 1.59) than if aged 25-34 years; and greater also than for males aged 35-44 years (HR = 1.59/1.25 or 1.27, 95% CI: 0.99 to 1.63). There is some indication that clients in qQ3 or qQ4 at accrual have reduced DRD-hazard (HR ~ 0.8) compared to qQ1. Clients whose prescription-source was non-GP had significantly higher DRD-risk (HR, 1.31).

For methadone-specific DRDs, interaction between gender and age-group is unnecessary; females have higher HR (1.4) than males; HRs increase very steeply with age-group at accrual, being 3-fold higher for clients 45+ years at accrual and 2-fold greater for clients aged 35-44 years than if 25-34 years old at accrual. Only the top quintile for quantity of prescribed methadone was associated with a significantly increased HR compared to qQ3.

Baseline quintile for recovered or actual daily-dose: For all DRDs, the significant gender by age-group interaction in **Table A3** confirms that females enjoy an importantly reduced DRD-risk under 35 years of age compared to males but, thereafter, the female advantage is neutralized. Males' DRD-risk increases significantly at 35+ years. The HR associated with dQ5, top quintile for daily-dose at first CHI-identified prescription, was significantly greater than for dQ3 (HR = 1.43/1.06 or 1.35; 95% CI: 1.00 to 1.81). Higher DRD-risk was associated with clients whose prescriber was other-source.

For methadone-specific DRDs, females are disadvantaged (HR 1.3, 95% CI: 1.0-1.6) and the steepness of increase in HRs, both age-related and by quintile for 1st daily-dose, is much greater than for all DRDs. By age-group, HR was 3-fold higher (95% CI: 2.4 to 4.2) at 45+ years of age than at 25-34 years. For dQ5, HR was also 3-fold higher (95% CI: 2.2 to 4.5) than for dQ1 and significantly greater than for dQ3 (HR = 3.15/1.68 or 1.88; 95% CI: 1.13 to 3.12), itself significantly greater than dQ1. Finally, higher HR for methadone-specific DRD was associated with other-source prescribers.

Table A2 Proportional hazards regressions for Scotland's 2009-2015 CHI-identified methadone-prescription cohort of 36,347 clients and 192,928 pys, incorporating quintiles for quantity of methadone prescribed at first CHI-identified methadone-prescription.

Quintiles for baseline quantity of prescribed methadone at 1st CHI-identified prescription				
Events	**1,323 DRDs**		**546 Methadone-specific DRDs**	
Covariates	Hazard ratio (HR)	95% CI for HR; p-value versus baseline	Hazard ratio (HR)	95% CI for HR; p-value versus baseline
qQ regression, 4df	***Chi-square 11.87; p ~ 0.018***		***Chi-square 33.40; p < 0.00001***	
Prescription-source (baseline: GP-prescriber)				
Other-source	1.31	1.17-1.47; p < 0.001	1.36	1.14-1.62; p ~ 0.001
Gender (baseline: male)				
Female	0.95	0.85-1.07	1.37	1.15-1.63; p < 0.001
Age-group at accrual (baseline: 25-34 years)				
< 25 years	0.72	0.56-0.94; p ~ 0.015	0.67	0.42-1.07
25-34	1.00		1.00	
35-44	1.38	1.23-1.56; p< 0.001	2.02	1.66-2.46; p < 0.001
45+ years	1.79	1.51-2.12; p <0.001	2.94	2.29-3.78; p < 0.001
Quintiles for prescribed quantity at accrual (qQ1 as baseline)				
qQ1: 5 - 270 mg	1.00		1.00	
qQ2: 271 - 645 mg	0.99	0.83-1.19	0.98	0.72-1.33
qQ3 646 - 1120 mg	0.80	0.67-0.96; p ~ 0.015	0.79	0.58-1.07
qQ4: 1121 - 1960 mg	0.83	0.70-0.99; p ~ 0.040	1.08	0.81-1.44
qQ5: > 1960 mg	0.97	0.81-1.15	1.61	1.22-2.11; p ~ 0.001
Now including interaction for gender by age-group at accrual on 3 degrees of freedom (df)				
Interaction regression chi-squared on 3df	***14.27; p ~ 0.0026***		***4.00; p ~ 0.26***	
Prescription-source (baseline: GP-prescriber)				
Other	1.31	1.17-1.47; p < 0.001	1.36	1.14-1.62; p ~ 0.001
Gender (baseline: male)				
Female	0.82	0.68-0.99; p ~ 0.035	1.21	0.89-1.66
Age-group at accrual (baseline: 25-34 years)				
< 25 years	0.92	0.66-1.28	0.84	0.44-1.62
25-34	1.00		1.00	
35-44	1.25	1.08-1.45; p ~ 0.002	1.81	1.40-2.32; p < 0.001
45+ years	1.59	1.30-1.95; p < 0.001	2.93	2.15-3.99; p < 0.001
Interaction between female & age-group at accrual (baseline: female & 25-34 years)				
< 25 years	0.61	0.36-1.05; p ~ 0.074	0.69	0.27-1.76
25-34	1.00		1.00	
35-44	1.37	1.06-1.78; p ~ 0.016	1.34	0.90-2.00
45+ years	1.46	1.02-2.10; p ~ 0.040	0.98	0.58-1.66
Quintiles for prescribed quantity at accrual (qQ1 as baseline)				
qQ1: 5 - 279 mg	1.00		1.00	
qQ2: 271 - 645 mg	0.99	0.83-1.19	0.98	0.72-1.33
qQ3: 646 - 1120 mg	0.80	0.67-0.96; p ~ 0.015	0.78	0.57-1.07
qQ4: 1121 - 1960 mg	0.83	0.70-0.99; p ~ 0.041	1.08	0.81-1.48; p ~ 0.001
qQ5: > 1960 mg	0.97	0.82-1.16	1.60	1.22-2.11; p ~ 0.001

Table A3: Proportional hazards regressions for Scotland's restricted 2009-2015 CHI-identified methadone-prescription cohort of 26,533 clients and 144,697 pys, with actual or recovered daily-dose of methadone prescribed at first CHI-identified methadone-prescription.

Quintiles for actual or recovered daily-dose of prescribed methadone at 1st CHI-identified prescription				
Events	**995 DRDs**		**420 Methadone-specific DRDs**	
Covariates	Hazard ratio (HR)	95% CI for HR; p-value versus baseline	Hazard ratio (HR)	95% CI for HR; p-value versus baseline
Prescription-source (baseline: GP-prescriber)				
Other-source	1.25	1.09-1.44; p ~ 0.001	1.32	1.07-1.63; p ~ 0.009
Gender (baseline: male)				
Female	0.92	0.80-1.05	1.29	1.05-1.58; p ~ 0.013
Age-group at accrual (baseline: 25-34 years)				
< 25 years	0.70	0.50-0.97; p ~ 0.033	0.67	0.38-1.19
25-34	1.00		1.00	
35-44	1.37	1.19-1.58; p< 0.001	2.00	1.60-2.50; p < 0.001
45+ years	1.91	1.58-2.31; p <0.001	3.15	2.37-4.19; p < 0.001
Quintiles for prescribed daily-dose at accrual (qQ1 as baseline)				
dQ1: [1 - 34.5] mg	1.00		1.00	
dQ2: (34.5 - 50] mg	1.10	0.89-1.35	1.39	0.95-2.04
dQ3 (50 - 70] mg	1.06	0.86-1.31	1.68	1.15-2.43; p ~ 0.007
dQ4: (70 - 90] mg	1.24	1.00-1.53; p ~ 0.046	2.16	1.49-3.13; p < 0.001
dQ5: > 90 mg	1.43	1.17-1.76; p ~ 0.001	3.15	2.21-4.48; p < 0.001
Now including interaction for gender by age-group at accrual on 3 degrees of freedom (df)				
Interaction regression chi-squared on 3df	***11.13; p ~ 0.011***		***6.52; p ~ 0.09***	
Prescription-source (baseline: GP-prescriber)				
Other	1.26	1.09-1.44; p ~ 0.001	1.33	1.08-1.64; p ~ 0.008
Gender (baseline: male)				
Female	0.78	0.63-0.98; p ~ 0.031	1.20	0.83-1.72
Age-group at accrual (baseline: 25-34 years)				
< 25 years	0.92	0.62-1.38	1.02	0.49-2.13
25-34	1.00		1.00	
35-44	1.23	1.04-1.46; p ~ 0.014	1.80	1.35-2.40; p < 0.001
45+ years	1.76	1.40-2.20; p < 0.001	3.34	2.37-4.70; p < 0.001
Interaction between female & age-group at accrual (baseline: female & 25-34 years)				
< 25 years	0.55	0.28-1.10	0.43	0.13-1.39
25-34	1.00		1.00	
35-44	1.42	1.05-1.92; p ~ 0.023	1.33	0.84-2.10
45+ years	1.32	0.86-2.02	0.78	0.42-1.47
Quintiles for prescribed daily-dose at accrual (qQ1 as baseline)				
dQ1: [1 - 34.5] mg	1.00		1.00	
dQ2: (34.5 - 50] mg	1.10	0.89-1.35	1.39	0.95-2.05
dQ3 (50 - 70] mg	1.06	0.86-1.31	1.67	1.15-2.43; p ~ 0.007
dQ4: (70 - 90] mg	1.24	1.00-1.53; p ~ 0.048	2.15	1.49-3.12; p < 0.001
dQ5: > 90 mg	1.43	1.16-1.76; p < 0.001	3.15	2.21-4.47; p < 0.001

Appendix3: Sensitivity analyses

Table A4: Proportional hazards regressions for Scotland's restricted 2009-2015 CHI-identified methadone-prescription cohort of 26,533 clients and 144,697 pys, with actual or recovered daily-dose of methadone prescribed at first CHI-identified methadone-prescription and current age-group.

Quintiles for daily-dose of prescribed methadone at 1st CHI-identified prescription				
Events	**995 DRDs**		**420 Methadone-specific DRDs**	
Covariates	Hazard ratio (HR)	95% CI for HR; p-value versus baseline	Hazard ratio (HR)	95% CI for HR; p-value versus baseline
dQ regression, 4df	***Chi-square 16.34; p ~ 0.0026***		***Chi-square 58.59; p < 0.00001***	
Prescription-source (baseline: GP-prescriber)				
Other-source	1.27	1.10-1.45; p ~ 0.001	1.34	1.08-1.65; p ~ 0.007
Gender (baseline: male)				
Female	0.92	0.80-1.06	1.28	1.05-1.56; p ~ 0.016
Current age-group (baseline: 25-34 years)				
< 25 years	0.71	0.43-1.16	0.58	0.23-1.43
25-34	1.00		1.00	
35-44	1.36	1.16-1.58; p< 0.001	1.70	1.32-2.18; p < 0.001
45+ years	2.10	1.77-2.50; p <0.001	3.15	2.40-4.13; p < 0.001
Quintiles for prescribed daily-dose at accrual (dQ1 as baseline)				
dQ1: [1 - 35] mg	1.00		1.00	
dQ2: (35 - 50] mg	1.09	0.89-1.34	1.42	0.98-2.06
dQ3 (50 - 70] mg	1.06	0.86-1.29	1.65	1.16-2.35; p ~ 0.006
dQ4: (70 - 90] mg	1.24	1.01-1.51; p ~ 0.043	2.11	1.49-3.01; p < 0.001
dQ5: > 90 mg	1.43	1.17-1.75; p < 0.001	3.10	2.22-4.33; p < 0.001
Now including interaction for gender by current age-group on 3 degrees of freedom (df)				
Interaction regression, 3df	***Chi-square 10.18; p ~ 0.017***		***Chi-square 6.49; p ~ 0.090***	
Prescription-source (baseline: GP-prescriber)				
Other	1.27	1.10-1.46; p ~ 0.001	1.34	1.08-1.65; p ~ 0.007
Gender (baseline: male)				
Female	0.70	0.54-0.91; p ~ 0.007	1.06	0.70-1.60
Current age-group (baseline: 25-34 years)				
< 25 years	0.93	0.51-1.72	1.16	0.42-3.20
25-34	1.00		1.00	
35-44	1.18	0.99-1.42	1.46	1.06-2.01; p ~ 0.020
45+ years	1.84	1.50-2.26; p < 0.001	2.97	2.12-4.16; p < 0.001
Interaction between female & current age-group (baseline: female & 25-34 years)				
< 25 years	0.58	0.21-1.61	0.18	0.02-1.65
25-34	1.00		1.00	
35-44	1.52	1.09-2.11; p ~ 0.013	1.46	0.88-2.43
45+ years	1.52	1.05-2.22; p ~ 0.028	1.12	0.64-1.97
Quintiles for prescribed daily-dose at accrual (dQ1 as baseline)				
dQ1: [1 - 34.5] mg	1.00		1.00	
dQ2: (34.5 - 50] mg	1.09	0.89-1.34	1.42	0.97-2.06
dQ3 (50 - 70] mg	1.06	0.86-1.29	1.65	1.15-2.35; p ~ 0.006
dQ4: (70 - 90] mg	1.23	1.01-1.51; p ~ 0.045	2.11	1.48-3.00; p < 0.001
dQ5: > 90 mg	1.43	1.17-1.74; p < 0.001	3.10	2.22-4.33; p < 0.001

Table A5: Proportional hazards regressions for Scotland's restricted 2009-2015 CHI-identified methadone-prescription cohort of 19,184 GP-clients and 107,284 pys, with actual or recovered daily-dose of methadone prescribed at first CHI-identified methadone-prescription and current age-group.

Quintiles for daily-dose of prescribed methadone at 1st CHI-identified prescription for GP-clients				
Events	**706 DRDs**		**293 Methadone-specific DRDs**	
Covariates	Hazard ratio (HR)	95% CI for HR; p-value versus baseline	Hazard ratio (HR)	95% CI for HR; p-value versus baseline
dQ regression, 4df	***Chi-square 14.45; p ~ 0.0060***		***Chi-square 44.60; p < 0.00001***	
Gender (baseline: male)				
Female	0.91	0.78-1.08	1.38	1.09-1.76; p ~ 0.008
Current age-group (baseline: 25-34 years)				
< 25 years	0.79	0.43-1.46	0.58	0.18-1.86
25-34	1.00		1.00	
35-44	1.30	1.08-1.57; p ~ 0.005	1.49	1.10-2.00; p ~ 0.009
45+ years	1.91	1.55-2.34; p <0.001	2.57	1.86-3.54; p < 0.001
Quintiles for prescribed daily-dose at accrual (dQ1 as baseline)				
dQ1: [1 - 35] mg	1.00		1.00	
dQ2: (35 - 50] mg	1.16	0.92-1.46	1.60	1.02-2.51; p ~ 0.040
dQ3 (50 - 70] mg	0.92	0.72-1.18	1.81	1.16-2.82; p ~ 0.009
dQ4: (70 - 90] mg	1.07	0.83-1.38	2.01	1.28-3.15; p ~ 0.003
dQ5: > 90 mg	1.40	1.10-1.77; p ~ 0.005	3.45	2.27-5.23; p < 0.001
Now including interaction for gender by current age-group on 3 degrees of freedom (df)				
Interaction regression, 3df	***Chi-square 9.43; p ~ 0.024***		***Chi-square 5.19; p ~ 0.158***	
Gender (baseline: male)				
Female	0.63	0.45-0.87; p ~ 0.005	0.90	0.54-1.50
Current age-group (baseline: 25-34 years)				
< 25 years	0.96	0.45-2.06	0.89	0.22-3.70
25-34	1.00		1.00	
35-44	1.11	0.89-1.38	1.16	0.80-1.69
45+ years	1.60	1.26-2.04; p < 0.001	2.11	1.42-3.13; p < 0.001
Interaction between female & current age-group (baseline: female & 25-34 years)				
< 25 years	0.72	0.20-2.57	0.44	0.04-5.16
25-34	1.00		1.00	
35-44	1.67	1.11-2.50; p ~ 0.013	1.86	1.00-3.43; p ~ 0.049
45+ years	1.78	1.13-2.81; p ~ 0.012	1.65	0.85-3.23
Quintiles for prescribed daily-dose at accrual (dQ1 as baseline)				
dQ1: [1 - 34.5] mg	1.00		1.00	
dQ2: (34.5 - 50] mg	1.16	0.92-1.46	1.60	1.02-2.51; p ~ 0.040
dQ3 (50 - 70] mg	0.93	0.72-1.19	1.81	1.16-2.82; p ~ 0.009
dQ4: (70 - 90] mg	1.07	0.83-1.37	2.00	1.27-3.13; p ~ 0.003
dQ5: > 90 mg	1.39	1.10-1.76; p ~ 0.006	3.44	2.27-5.22; p < 0.001

Table A6: Proportional hazards regression for methadone-specific DRDs: 16,350 clients in Scotland's 2009-2015 CHI-identified methadone-prescription cohort with actual or recovered daily-dose of methadone at first CHI-identified methadone-prescription and cohort-entry in July to December 2009; 102,566 pys of follow-up.

Quintiles for actual or recovered daily-dose of methadone at 1st CHI-identified prescription (dQ) dQ regression chi-square of 49.31 on 4 degrees of freedom; p < 0.00001		
Events	**295 Methadone-specific DRDs**	
Covariates [clients, %]	Hazard Ratio (HR)	95% confidence interval for HR; p-value versus baseline
Prescription-source (baseline: GP-prescriber)		
Other-source [3036, 19%]	**1.00**	0.74-1.35; p ~ 0.995
Gender (baseline: male)		
Female [5502, 34%]	**1.28**	1.01-1.63; p ~ 0.040
Age-group at accrual (baseline: 25-34 years)		
< 25 years [796, 5%]	**0.29**	0.09-0.93; p ~ 0.037
25-34 [7105, 43%]	**1.00**	**Baseline**
35-44 [6717, 41%]	**1.71**	1.32-2.23; p < 0.001
45+ years [1732, 11%]	**2.59**	1.84-3.65; p < 0.001
Quintiles for prescribed quantity at accrual (qQ1 as baseline)		
dQ1: [1 - 34.5] mg [2608, 16%]	**1.00**	**Baseline**
dQ2: (34.5 - 50] mg [3394, 21%]	**1.80**	1.07-3.04; p ~ 0.028
dQ3 (50 - 70] mg [3768, 23%]	**2.18**	1.32-3.61; p ~ 0.002
dQ4: (70 - 90] mg [3253, 20%]	**2.45**	1.48-4.06; p ~ 0.001
dQ5: > 90 mg [3327, 20%]	**4.03**	2.50-6.52; p < 0.001

Table A7: Proportional hazards regression for methadone-specific DRDs: 10,183 clients Scotland's 2009-2015 CHI-identified methadone-prescription cohort with actual or recovered daily-dose of methadone at first CHI-identified methadone-prescription and cohort-entry after 2009; 42,131 pys of follow-up.

Quintiles for actual or recovered daily-dose of methadone at 1st CHI-identified prescription (dQ) dQ regression chi-square of 16.20 on 4 degrees of freedom; p ~ 0.0028		
Events	**125 Methadone-specific DRDs**	
Covariates [clients, %]	Hazard Ratio (HR)	95% confidence interval for HR; p-value versus baseline
Prescription-source (baseline: GP-prescriber)		
Other-source [4313, 42%]	**1.80**	1.25-2.61; p ~ 0.002
Gender (baseline: male)		
Female [3242, 32%]	**1.35**	0.93-1.96; p ~ 0.116
Age-group at accrual (baseline: 25-34 years)		
< 25 years [1195, 12%]	**1.24**	0.60-2.54; p ~ 0.564
25-34 [4462, 44%]	**1.00**	**Baseline**
35-44 [3337, 33%]	**2.92**	1.88-4.54; p < 0.001
45+ years [1189, 12%]	**4.97**	2.92-8.44; p < 0.001
Quintiles for prescribed quantity at accrual (qQ1 as baseline)		
dQ1: [1 - 34.5] mg [2699, 27%]	**1.00**	**Baseline**
dQ2: (34.5 - 50] mg [2893, 28%]	**0.97**	0.54-1.74; p ~ 0.910
dQ3 (50 - 70] mg [2124, 21%]	**1.11**	0.61-2.02; p ~ 0.733
dQ4: (70 - 90] mg [1392, 14%]	**2.08**	1.17-3.68; p ~ 0.012
dQ5: > 90 mg [1075, 11%]	**2.25**	1.25-4.05; p ~ 0.007