Mortality risk of opioid substitution therapy with methadone versus buprenorphine: a retrospective cohort study

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Summary

Background **Opioid dependence increases risk of premature mortality. Opioid substitution therapy with methadone or buprenorphine reduces mortality risk, especially for drug-related overdose. Clinical guidelines recommend methadone as the first line of opioid substitution therapy. We aimed to test whether buprenorphine treatment has a lower mortality risk than does methadone treatment by comparing all-cause mortality and drug-related overdose mortality at treatment induction, after in-treatment medication switches, and following treatment cessation.**

Methods **We did a retrospective cohort study of all patients with opioid dependency (n=32 033) in New South Wales, Australia, who started a methadone or buprenorphine treatment episode from Aug 1, 2001, to Dec 31, 2010, including 190 232·6 person-years of follow-up. We compared crude mortality rates (CMRs) for all-cause and drug-related overdose mortality, and mortality rate ratios (MRRs) according to age, sex, period in or out of treatment, medication type, and in-treatment switching.**

Findings **Patients who initiated with buprenorphine had reduced all-cause and drug-related mortality during the first 4 weeks of treatment compared with those who initiated with methadone (adjusted all-cause MRR 2·17, 95% CI 1·29–3·67; adjusted drug-related MRR 4·88, 1·73–13·69). For the remaining time on treatment, drug-related mortality risk did not differ (adjusted MRR 1·18, 95% CI 0·89–1·56), but weak evidence suggested that all-cause mortality was lower for buprenorphine than methadone (1·66, 1·40–1·96). In the 4 weeks after treatment cessation, all-cause mortality did not differ, but drug-related mortality was lower for methadone (adjusted all-cause MRR 1·12, 0·79–1·59; adjusted drug-related MRR 0·50, 0·29–0·86). Patients who switched from buprenorphine to methadone during treatment had lower mortality in the first 4 weeks of methadone treatment than matched controls who received methadone only (CMR difference 7·1 per 1000 person-years, 95% CI 0·1–14·0); no mortality difference was noted for switches from buprenorphine to methadone or for switches to either medication beyond the first 4 weeks of treatment.**

Interpretation **In a setting with high risk of death in the first 4 weeks of opioid substitution therapy, buprenorphine seemed to reduce mortality in this period, but little difference between buprenorphine and methadone was noted thereafter or for in-treatment switching of medications. Cross-cohort corroboration of our findings and further assessment of the stepped treatment model is warranted.**

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Introduction

Opioid dependence increases risk of premature mortality.[1] Leading causes of death among dependent or regular users of opioids include unintentional drug overdose, suicide and other injury, and sequelae of HIV and hepatitis C infection.[1] Opioid substitution therapy greatly improves survival of individuals with opioid dependency who are in treatment by reducing mortality risk, especially for mortality due to fatal opioid-related overdose.[2–5] Nonetheless, mortality risk remains high during the 4 weeks after treatment induction and treatment cessation.[3,6]

Methadone and buprenorphine, two opioid substitution pharmacotherapies, are WHO essential medicines.[7] As a partial opioid receptor agonist, buprenorphine is less likely to induce respiratory depression than is methadone, and might pose a lower risk of opioid overdose, especially during treatment induction[8,9] or unsanctioned opioid use during opioid substitution therapy.[10] Ecological data from France show a strong correlation between an increase in buprenorphine treatment and reduction in drug overdose deaths.[11] However, no direct clinical trial evidence exists that is sufficiently powered to compare risk of death between buprenorphine and methadone.[6] Previous comparisons suggest that retention might be poorer for buprenorphine than for methadone[12–15] and that patients receiving buprenorphine are more likely to switch medications during treatment.[14,15] Clinical guidance recommends methadone as the first line of treatment instead of buprenorphine because it is more cost effective.[16,17] In the USA, variations in reimbursement of treatment costs have also affected prescribing preferences.[18–20] However, methadone, a full opioid agonist, can cause potentially hazardous respiratory depression during treatment induction. The first 4 weeks of treatment in particular might pose an excess risk of mortality from opioid overdose compared with the remainder of time on treatment.[3,21–23]

To date, however, no well powered studies have been done to directly compare the mortality risks in different

See Online for appendix

Research in context

Evidence before this study

We searched PubMed from inception up to April 2, 2015, for studies comparing all-cause mortality or drug-related mortality risk of patients on buprenorphine and methadone. We used the search terms "buprenorphine", "methadone", and "mortality" with no language restrictions and restricted our search to comparative studies. We reviewed 7 studies from 103 results (appendix) but identified no well powered direct comparison of risk of all-cause or drug-related overdose mortality at different periods of buprenorphine and methadone treatment.

Added value of this study

Only large observational studies can detect a sufficient number of deaths to guide clinicians on which treatments are safest. Our study represents the most detailed and well powered study so far of potential differences in mortality risk between individuals receiving buprenorphine and those receiving methadone for opioid dependence during specific periods in and out of treatment. We report that the risk of drug-related overdose mortality and all-cause mortality during the first 4 weeks of treatment induction is increased for patients commencing methadone compared with those commencing buprenorphine. Sensitivity analyses suggested that this differential mortality risk was unlikely to be caused by unmeasured confounding. For patients who switched to methadone after already having been stabilised on buprenorphine, no such comparative elevation in risk existed. Evidence of differential risk between methadone and buprenorphine in drug-related overdose mortality or all-cause mortality at other periods during and after treatment was less compelling or consistent.

Implications of all available evidence

Our findings have direct clinical relevance, suggesting that induction of patients on to buprenorphine is beneficial in settings in which risk of death is increased in the first 4 weeks of treatment, but thereafter little evidence suggests any difference in mortality risk by treatment type or in switching medications. Cross-cohort analyses to corroborate our findings are warranted. Findings from past research show the importance of treatment duration in reduction of drug-related mortality, and increased average treatment durations for methadone compared with buprenorphine have outweighed the slightly reduced mortality risk during buprenorphine treatment compared with methadone treatment. Our findings are consistent with a stepped approach for methadone treatment whereby patients are first induced on to buprenorphine and then transferred to methadone. Further assessment of optimum induction practice, treatment outcomes, and mortality risk is warranted.

periods in and out of treatment for these two medications for use in opioid substitution therapy,[6] nor to compare in-treatment switching between buprenorphine and methadone. In this study we investigated whether risk of all-cause mortality and unintentional drug-related overdose mortality differed between buprenorphine and methadone at various periods and stages of opioid substitution therapy.

Methods

Study population

We used unit records from the Pharmaceutical Drugs of Addiction System (PHDAS; appendix), the administrative database of the New South Wales (NSW) Opioid Substitution Treatment Program, to establish a retrospective cohort of people with opioid dependency who started a treatment episode of opioid substitution therapy from Aug 1, 2001, to Dec 31, 2010. As in previous studies,[3,14] we excluded individuals who did not commence treatment, those in temporary programmes such as interstate patients, those in withdrawal programmes, and participants in clinical trials of buprenorphine because they were not necessarily given buprenorphine. We defined a new treatment episode as one that started 7 or more days after a previous episode had finished.[3,14] We deemed a change or switch in the medication dispensed within a treatment episode to represent a continuous episode if there was less than 7 days between the end of one episode and the start of the next.

In allocating deaths to in-treatment or out-of-treatment time periods, we treated the 6 days after the end of a treatment programme as part of that programme.[3,14] Any potential bias from this definition, which allocates some deaths that occurred after leaving treatment to the treatment period, will bias in-treatment mortality upwards and out-of-treatment mortality downwards, resulting in conservative estimates of mortality reduction during treatment.

The PHDAS unit records were linked to the National Death Index (NDI; appendix) by staff at the Australian Institute of Health and Welfare using an in-house probabilistic record linkage program. Matching variables included full name, date of birth, sex, and date and state of last known contact. Causes of death were coded using ICD-10 codes,[24] and up to 19 contributing causes of death were coded. Unintentional drug-related overdose deaths, split into all, opioid, and non-opioid, were defined as in previous studies.[3,25]

Ethical approval was obtained from institutional review boards at the University of NSW (HC12019), NSW Health—Population and Health Services (2011/11/360), Australian Institute of Health and Welfare (EC2011/2/13), the Alfred Hospital (165/11), Corrective Services NSW (11/82607), NSW Justice Health (G219/11), the Aboriginal Health and Medical Research Council (793/11), and the Victorian Department of Justice Health (CF/13/3440). Ethics committees gave exemption for consent due to use of anonymised data.

Statistical analysis

We calculated crude mortality rates (CMRs) for deaths from any cause and drug-related overdose deaths using the number of deaths and the number of person-years of follow-up. Person-years were calculated from the first treatment episode commenced since Aug 1, 2001, until death or Dec 31, 2010, whichever occurred first.

We calculated CMRs by age group (<30 years, 30–39 years, and ≥40 years), sex, and medication type (methadone *vs* buprenorphine) for the first 4 weeks in a treatment episode, the remaining time in the same treatment episode (until the end of that treatment episode or end of follow-up, whichever came first), the first 4 weeks out of a treatment episode, and remaining time out of that treatment episode (until the start of next treatment episode, death, or end of follow-up, whichever came first), similar to previous studies.[3,6,26]

We used Poisson regression to estimate all-cause and drug-related mortality rate ratios (MRRs) and to test whether the risk of death during periods in and out of treatment differed by treatment modality (methadone *vs* buprenorphine), adjusted for potential confounders (age, sex). We grouped age into three categories (<30 years, 30–39 years and ≥40 years). To ensure that there was no residual confounding of the methadone–buprenorphine association due to the grouping of the age variable, fractional polynomial regression was done and the optimum functions for continuous age were added to the mortality models. These did not make an important improvement to the model fit or change the methadone–buprenorphine association, and were therefore replaced by the age group variable in the final models. In exploratory analyses, we assessed variation in mortality risk by calendar period for the first 5 years after the introduction of buprenorphine treatment to the NSW opioid substitution therapy programme compared with the subsequent 5 years of buprenorphine treatment (2001–05 *vs* 2006–10) and we detected no difference in mortality risk after adjustment for age and sex (likelihood ratio test p=0·1219).

We used a nested cohort design to compare the risk of mortality in patients who switched medications during a treatment episode and in patients who remained on a single medication throughout a treatment episode. Each patient who switched medication was matched by age and sex with two patients who did not switch. We compared the mortality risk difference in the first 4 weeks after switching from buprenorphine to methadone with the risk of death in the first 4 weeks of induction on methadone, and the risk of death during the remaining time on treatment for patients who switched from buprenorphine to methadone versus those who were initiated and remained on methadone. We also did the corresponding comparisons for patients who switched from methadone to buprenorphine. Person-years after the switch were allocated to the new medication, both during treatment and after treatment.

We did sensitivity analyses for the primary in-treatment and out-of-treatment mortality analyses to investigate the possibility that any significant effects from the medications could have been caused by confounding by indication. The prevalence of some confounders would likely differ between the methadone and buprenorphine groups, but the extent of the imbalance was unknown. With our sensitivity analyses, we aimed to establish how strong the residual confounding would have to be to explain the effect sizes.[27] The sensitivity analyses needed information about the prevalence of the confounder in the population, the imbalance in prevalence of the confounder in the two medication groups, and the relative risk of mortality for individuals with the confounder.

First, we searched the scientific literature to assess the prevalence of unmeasured confounders that could increase mortality risk and the estimated level of this increased mortality risk. Our search suggested concomitant benzodiazepine use or misuse (prevalence 64%, hazard ratio (HR) 1·34[28]), lifetime psychiatric admission (33%, HR 6·93;[28] 49%, HR 2·46[29]), overdose history (25%, HR 1·68;[30] 54%, HR 3·69[31]), prison history of more than 1 year (23%, HR 1·98[30]), and high comorbidity score (5%, HR 2·61;[29] 17%, MRR 2·40[6]) as potential confounders. From these estimates, we did the sensitivity analysis by assuming a prevalence of 50% for the potential unmeasured confounder in the methadone group and varying its prevalence in the buprenorphine group from 50% to 0% (for comparisons with an MRR of more than 1) or from 50% to 100% (for comparisons with an MRR of less than 1) or until the effect reached the null (ie, MRR of 1), and repeated for three estimated levels of relative risk (RR) of mortality for the confounder of 2, 4, and 6. We did the sensitivity analyses with Microsoft Excel 2010 and the main analyses with SAS 9.3.

Role of the funding source

The funders of the study had no role in study design, data analysis, data interpretation, or writing of the report. All authors had full access to all the data in the

	Person-years	Deaths	CMR (95% CI)
Total population	190 232·6	1600	8·4 (8·0–8·8)
Sex			
Men	127 706·8	1167	9·1 (8·6–9·7)
Women	62 525·8	433	6·9 (6·3–7·6)
Age group (years)			
<30	52 417·3	276	5·3 (4·7–5·9)
30–39	72 966·0	507	6·9 (6·4–7·6)
≥40	64 849·2	817	12·6 (11·7–13·5)
Calendar period			
2001–05	59 869·2	426	7·1 (6·5–7·8)
2006–10	130 363·4	1174	9·0 (8·5–9·5)

CMR=crude mortality rate per 1000 person-years.

Table 1: **Patient characteristics and mortality**

study and had final responsibility for the decision to submit for publication.

Results

32 033 people entered at least one episode of opioid substitution therapy in NSW between Aug 1, 2001, and Dec 31, 2010, giving a total of 190 232·6 person-years of follow-up (median 6·7 years per person, IQR 3·7–8·4) and 71 439 episodes of treatment. Median length of completed treatment episodes (ie, episodes that were not ongoing at end of follow-up) was 137 days (IQR 22–513) and patients entered a mean of 2·2 (SD 2·0, range 1–24) treatment episodes. Median time out of treatment after leaving treatment and before returning to treatment or end of follow-up was 95 days (IQR 29–296).

Methadone was the first medication prescribed in 42 203 (59·1%) treatment episodes. During the study period, 5971 (18·6%) patients switched medications during a treatment episode on 8586 occasions. In 4594 (53·5%) of these medication switch occasions, the switch was from methadone to buprenorphine, with the remaining 3992 (46·5%) switches being from buprenorphine to methadone.

During the follow-up period, 1600 deaths occurred, with an overall CMR of 8·4 deaths per 1000 person-years (95% CI 8·0–8·8). CMRs were higher in men than in women, in older age groups than in younger age groups, and in 2006–10 than in 2001–05 (table 1). The most common cause of death was unintentional drug-related overdose (697 [43·6%] deaths).

All-cause mortality and drug-related overdose mortality were higher for methadone than for buprenorphine during the first 4 weeks in treatment (table 2). The all-cause CMR for the first 4 weeks on methadone was 9·6 per 1000 person-years, compared with 4·3 per 1000 person-years in the first 4 weeks of buprenorphine (adjusted MRR 2·17; 95% CI 1·29–3·67). MRRs showed that risk of drug-related overdose was nearly five times higher for methadone than for buprenorphine (table 2).

For the remaining time on treatment, the all-cause CMR for methadone was 6·8 per 1000 person-years, compared with 3·9 per 1000 person-years for buprenorphine (adjusted MRR 1·66, 95% CI 1·40–1·96). Rates of drug-related overdose mortality did not significantly differ by medication type during the remaining time in treatment in adjusted analyses (table 2).

Mortality risk was raised in the first 4 weeks out of treatment compared with mortality risk during treatment (table 2). All-cause CMR did not significantly differ between methadone and buprenorphine in this period. By contrast, during the first 4 weeks out of treatment, the drug-related overdose mortality risk was

	Methadone			Buprenorphine			MRR (95% CI)	Adjusted MRR* (95% CI)
	Person-years	Deaths	CMR (95% CI)	Person-years	Deaths	CMR (95% CI)		
In-treatment period								
First 4 weeks								
All	3343·9	32	9·6 (6·5–13·5)	2094·3	9	4·3 (2·0–8·2)	2·22 (1·71–2·89)	2·17 (1·29–3·67)
Drug related		18	5·4 (3·2–8·5)		2	1·0 (0·1–3·4)	5·14 (3·07–8·62)	4·88 (1·73–13·69)
Opioid		14	4·2 (2·3–7·0)		1	0·5 (0·01–2·7)	8·00 (3·91–16·4)	7·61 (1·81–31·94)
Other drug		4	1·2 (0·3–3·1)		1	0·5 (0·01–2·7)	2·29 (1·05–4·96)	2·12 (0·45–9·96)
Remainder								
All	88 448·5	604	6·8 (6·3–7·4)	19 841·9	78	3·9 (3·1–4·9)	1·74 (1·60–1·89)	1·66 (1·40–1·96)
Drug related		151	1·7 (1·4–2·0)		29	1·5 (1·0–2·1)	1·17 (1·02–1·34)	1·18 (0·89–1·56)
Opioid		124	1·4 (1·2–1·7)		24	1·2 (0·8–1·8)	1·16 (0·99–1·35)	1·17 (0·86–1·60)
Other drug		27	0·3 (0·2–0·4)		5	0·3 (0·1–0·6)	1·21 (0·86–1·70)	1·19 (0·61–2·35)
Out-of-treatment period								
First 4 weeks								
All	1835·5	35	19·1 (13·3–26·5)	1673·6	28	16·7 (11·1–24·2)	1·14 (0·96–1·36)	1·12 (0·79–1·59)
Drug related		10	5·4 (2·6–10·0)		18	10·8 (6·4–17·0)	0·50 (0·38–0·66)	0·50 (0·29–0·86)
Opioid		7	3·8 (1·5–7·9)		13	7·8 (4·1–13·3)	0·49 (0·35–0·68)	0·48 (0·25–0·93)
Other drug		3	1·6 (0·3–4·8)		5	3·0 (1·0–7·0)	0·54 (0·33–0·90)	0·54 (0·19–1·48)
Remainder								
All	43429·6	528	12·2 (11·1–13·2)	29 565·3	286	9·7 (8·6–10·9)	1·26 (1·19–1·32)	1·23 (1·11–1·36)
Drug related		206	4·7 (4·1–5·4)		125	4·2 (3·5–5·0)	1·12 (1·04–1·21)	1·12 (0·96–1·31)
Opioid		175	4·0 (3·5–4·7)		110	3·7 (3·1–4·5)	1·08 (1·00–1·18)	1·08 (0·92–1·28)
Other drug		31	0·7 (0·5–1·0)		15	0·5 (0·3–0·8)	1·41 (1·13–1·75)	1·39 (0·90–2·14)

CMR=crude mortality rate per 1000 person-years. MRR=mortality rate ratio. *Adjusted for age group and sex.

Table 2: **All-cause deaths and unintentional drug-related overdose deaths by treatment and treatment period**

lower for methadone treatment than for buprenorphine treatment (table 2).

In the remaining time out of treatment, patients out of methadone treatment had a small increase in all-cause mortality compared with patients out of buprenorphine treatment (table 2). However, after adjustment for age and sex, unintentional drug-related overdose mortality did not differ significantly between the two medications for the remaining time out of treatment.

For in-treatment switches, no deaths occurred in the first 4 weeks after switching from buprenorphine to methadone (288·8 person-years of follow-up), compared with four deaths in the same period in matched methadone-only controls (567·6 person-years of follow-up; CMR difference 7·05 [95% CI 0·14–13·95]). No patients died in the 4 weeks following in-treatment switches from methadone to buprenorphine, or in the 4 weeks after treatment induction for the matched buprenorphine-only control group. For the remaining time within treatment episodes, mortality rates did not differ significantly between patients who had switched from buprenorphine to methadone or from methadone to buprenorphine compared with the respective matched single-medication control groups (table 3).

In our sensitivity analyses, we assessed whether the calculated MRRs would change after increasing the imbalance in prevalence of a hypothetical unmeasured confounder in the buprenorphine group (figure). For the all-cause MRR (2·17) in the first 4 weeks of treatment, in order for all of the increased rate of mortality in the methadone group to be explained, the relative risk of mortality for the confounder would have to be at least 4 and the prevalence in the buprenorphine group would need to be less than 10% (compared with 50% in the methadone group; figure). The drug-related MRR of 4·88 in the first 4 weeks of treatment could not be explained by any sensitivity analysis scenarios; the effect remained above 1, even with a relative risk of mortality of 6 and maximum imbalance in the confounder. The all-cause MRR of 1·66 in the remaining time in treatment needed the relative risk of mortality to be 4 and the prevalence of the confounder to be less than 20% in the buprenorphine group to reach the null. The drug-related MRR in the first 4 weeks out of treatment was in the opposite direction to the other significant associations, with the mortality higher in the buprenorphine group than in the methadone group. Consequently, the sensitivity analysis assumed an increasing prevalence of the mortality-associated confounder in the buprenorphine group. However, even with the maximum imbalance in the confounder and the highest confounder relative risk of mortality of 6, this effect did not reach the null. The smaller all-cause MRR of 1·26 for the remaining time out of treatment was not as robust as the other effects and moved to the null when confounder prevalence in the buprenorphine group was 35% for a relative risk of mortality of 6 and 19% for a relative risk of 2.

	Person-years	Deaths	CMR (95% CI)	CMR difference (95% CI)†
First 4 weeks on opioid substitution treatment				
Methadone				
Methadone only	567·6	4	7·1 (1·9 to 18·0)	..
After a switch from buprenorphine	288·8	0	0 (0 to 12·8)*	7·1 (0·1 to 14·0)
Buprenorphine				
Buprenorphine only	525·6	0	0 (0 to 7·0)*	..
After a switch from methadone	294·8	0	0 (0 to 12·5)*	..
Remainder of time on opioid substitution treatment				
Methadone				
Methadone only	17 692·6	66	3·7 (2·9 to 4·8)	..
After switch from buprenorphine	6983·5	22	3·2 (2·0 to 4·8)	–0·6 (–2·2 to 1·0)
Buprenorphine				
Buprenorphine only	6888·6	18	2·6 (1·6 to 4·1)	..
After a switch from methadone	3538·3	10	2·8 (1·4 to 5·2)	0·2 (–1·9 to 2·3)

Methadone-only and buprenorphine-only data given for age-matched and sex-matched controls (two per switched patient). CMR=crude mortality rate per 1000 person-years. *One-sided 97·5% CI. †Difference in CMR between switched patients and matched controls.

Table 3: **Mortality risk after an in-treatment medication switch compared with methadone-only or buprenorphine-only treatment induction**

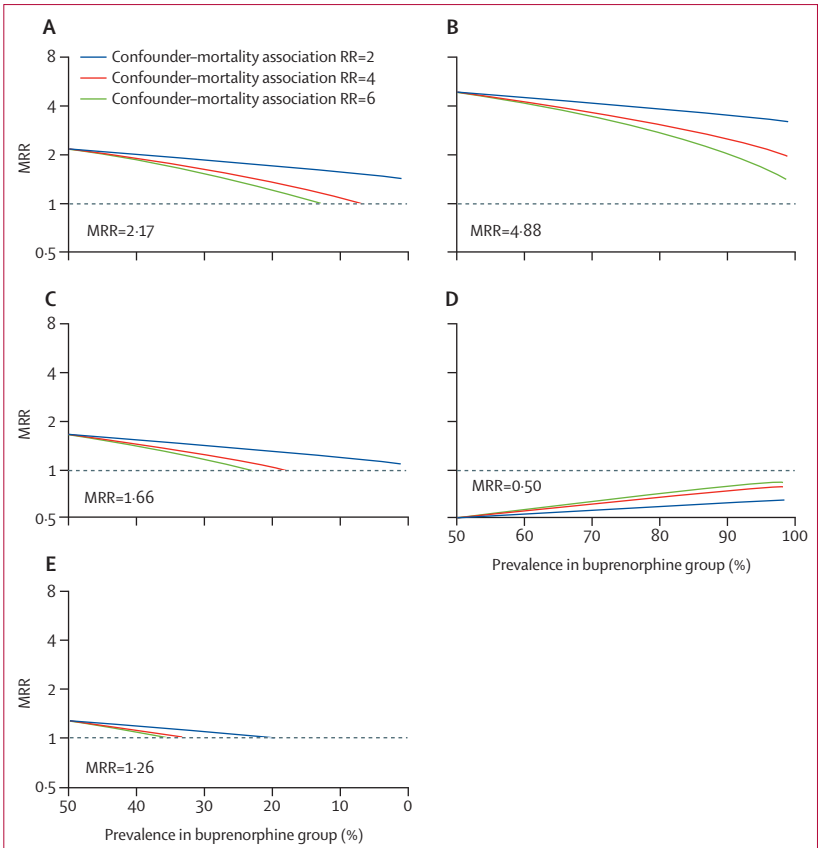

Figure: **Degree of change in the true MRR with sensitivity analysis scenarios**
All-cause mortality in the first 4 weeks of treatment (A); drug-related mortality in the first 4 weeks of treatment (B); all-cause mortality in the remainder of treatment (C); drug-related mortality in the first 4 weeks out of treatment (D); all-cause mortality in the remaining time out of treatment (E). RR=relative risk. MRR=mortality rate ratio.

Discussion

We identified strong evidence that the risk of drug-related overdose during the first 4 weeks of treatment induction and stabilisation is almost five times higher, and all-cause mortality double, for patients inducted on to methadone than for those inducted on to buprenorphine. By contrast, if a patient switched to methadone after already having been stabilised on buprenorphine, there was no such comparative elevation in risk. These patients also had a reduced rate of mortality compared with those inducted on to a methadone-only treatment episode.

The evidence for a differential risk between methadone and buprenorphine in overdose or all-cause mortality at other periods during and after treatment is less compelling or consistent. Drug-related overdose did not seem to differ between methadone and buprenorphine during the remaining time on treatment, and, although all-cause mortality showed a significant difference, this association was weak with a small effect size that was not robust to unmeasured confounder analysis. After patients left treatment, the evidence was inconsistent. Although the risk of unintentional drug-related overdose mortality in the first 4 weeks after treatment was halved for patients leaving methadone compared with those leaving buprenorphine, we did not see a difference between methadone and buprenorphine in the risk of all-cause mortality in this crucial period. A lower mortality rate in 2001–05 than in 2006–10 shows the effects of a heroin shortage in the study region on drug-related deaths in the earlier period.[32,33]

We acknowledge several limitations to our study. First, we did not have detailed patient and treatment characteristics. Patients who entered methadone and buprenorphine treatment and those who switched medications are unlikely to be identical, so confounding by indication might have biased the findings. However we tried to account for potential confounders missing from our dataset—such as co-prescription of benzodiazepines, mental and physical comorbidity, previous overdose, and prison history[6,28,29,31,34,35]—to establish to what extent imbalance in these confounders could explain any difference in mortality risk for patients prescribed methadone or buprenorphine at specific times on or off treatment. Our sensitivity analysis suggests that the reduction in mortality risk for patients on buprenorphine compared with those on methadone at treatment initiation is unlikely to be caused by unmeasured confounding. However, the comparatively smaller increases in all-cause mortality risk for methadone compared with buprenorphine that were recorded for the remaining time in treatment and remaining time out of treatment must be treated cautiously. A moderate imbalance in confounders could reduce these associations to the null, and we noted no increase in unintentional drug-related overdose deaths, suggesting that this effect was not a direct effect of the medications. Additionally, we have not explored the potential effects of any interaction between confounders which might affect the mortality effect sizes, although the differences at treatment initiation are unlikely to be reversed or nullified. The inconsistency between risk of all-cause mortality (adjusted MRR 1·12) and drug-related overdose mortality (0·50) in the first 4 weeks after treatment with methadone or buprenorphine and our sensitivity testing suggest that some of the excess overdose risk for patients prescribed buprenorphine probably results from unmeasured confounding. Alternatively, patients on buprenorphine might have an increased risk of overdose because of high rates of relapse in the first month after treatment cessation (as suggested by shorter periods of opioid substitution therapy and higher rates of treatment dropout for patients on buprenorphine than for patients on methadone).[14] Further cross-cohort analyses are needed to corroborate our findings and test this hypothesis.

Second, because information about individual dose, treatment plans, and delivery were unavailable, we were unable to establish the reason for treatment switching or characterise and test whether treatment performance (such as graduated induction, optimum dosing, supervised consumption, and psychosocial therapies) affected treatment retention and mortality risk.[15] Our findings are summary effects for varied settings, dosing strategies, and performance, and might not represent the potential effect of optimum opioid substitution therapy provision.

Third, our analyses comparing the mortality risk of patients who switched medications within a treatment episode with that of patients who received a single medication might have been underpowered. Although we detected differences in mortality risk for people switching from buprenorphine to methadone compared with those who underwent induction with methadone only, the number of deaths was small and people who switch might be more likely to be stable than are those who are starting treatment. Further assessment of the effect of switching opioid substitution medications through pooling of mortality cohorts is needed.

To our knowledge, this study represents the most detailed and well powered study so far of the potential differences in mortality risk for individuals receiving buprenorphine and those receiving methadone for opioid dependence during specific periods in and out of the treatment. Although the limitations we have described might suggest that evidence from randomised trials is needed to corroborate our findings, this is unlikely to happen for several reasons. First, trials of the effects of opioid substitution therapy on mortality and drug-related deaths are not ethical if medications are compared against no treatment or placebo, because methadone and buprenorphine are classified as WHO essential medicines.[7] Second, no previous trials of opioid substitution therapy alone or in meta-analyses have ever had sufficient power to detect differences in

mortality risk and, therefore, any future trial—eg, of buprenorphine versus methadone—is unlikely to be large enough to test our findings.[1,13] Only large observational studies such as this one can detect a sufficient number of deaths to guide clinicians on which treatments and delivery models are safest, and studies elsewhere should seek to test our findings. Second, confounding by indication is an important problem in all observational studies: in this case between patients selected to receive methadone and those selected to receive buprenorphine. For this reason, we did sensitivity analyses to assess the robustness of the findings, and likelihood that an additional confounder would nullify the results. We show that our main finding—that buprenorphine reduces risk of death in the first 4 weeks of treatment compared with methadone—is robust. Third, if the reduced risk of death in first 4 weeks of treatment was caused by selection bias towards prescription of buprenorphine to patients who had a lower risk of death and higher likelihood of treatment compliance than those of patients prescribed methadone, we would expect that the risk of death during the rest of the time on treatment and after treatment would also favour buprenorphine. This was not the case in our analyses.

Clinicians providing opioid substitution treatment face an important dilemma: which is more likely to reduce patient risk, buprenorphine or methadone? Buprenorphine is argued to have a superior safety profile to methadone but also has a higher dropout rate. Our data suggest that induction of patients on to buprenorphine has clear benefits in settings in which risk of death is elevated in the first 4 weeks of treatment, such as Australia and the UK,[3,6] but thereafter little evidence exists for any difference in mortality risk or dangers in switching opioid substitution therapy. This finding has direct clinical relevance to clinicians, patients, and policy makers worldwide.

Other studies,[14,15] however, have raised concerns about reduced treatment retention for patients on buprenorphine compared with those on methadone. Treatment duration is crucial to prevention of drug-related deaths.[36] In a previous study,[14] we estimated that the increased average treatment duration for methadone compared with buprenorphine outweighed the slightly reduced mortality risk during buprenorphine treatment.[3] However, our findings are consistent with, and support, a stepped treatment approach for methadone treatment whereby patients are first induced on to buprenorphine and subsequently transferred to methadone. Notably, a randomised trial[37] of stepped methadone treatment (buprenorphine/naloxone to methadone) and conventional methadone treatment reported that treatment retention, opioid use, and addiction severity were equivalent at 6 months. Further assessment of the optimum induction practice, treatment outcomes, and mortality risk is warranted.

Contributors
JK, LD, and MH conceived the study. SL, DR, and JK did the statistical analysis and all authors had full access to the data. JK drafted the manuscript with LD, MH, SL, and DR. All authors contributed to and approved the final manuscript. LD is the study guarantor.

Declaration of interests
LD has received untied educational grants from Reckitt Benckiser for the post-marketing surveillance of opioid substitution therapy medications in Australia, the development of an opioid-related behaviour scale, and a study of opioid substitution therapy uptake among chronic non-cancer pain patients; untied educational grants from Mundipharma to conduct surveillance of the use of OxyContin in Australia; and travel costs from Pfizer and Mundipharma for presenting invited talks at conferences. The other authors declare no competing interests.

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