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Mortality among clients of a state-wide opioid pharmacotherapy program over 20 years: Risk factors and lives saved☆

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ABSTRACT

Background: The small size of previous studies of mortality in opioid dependent people has prevented an assessment of the extent to which elevated mortality risks are consistent across time, clinical and/or patient groups. The current study examines reductions in mortality related to treatment in an entire treatment population.
Methods: Data from the New South Wales (NSW) Pharmaceutical Drugs of Addiction System, recording every "authority to dispense" methadone or buprenorphine as opioid replacement therapy, 1985–2006, was linked with data from the National Deaths Index, a record of all deaths in Australia. Crude mortality rates and standardized mortality ratios were calculated according to age, sex, calendar year, period in- or out-of-treatment, medication type, previous treatment exposure and cause of death.
Results: Mortality among 42,676 people entering opioid pharmacotherapy was elevated compared to age and sex peers. Drug overdose and trauma were the major contributors. Mortality was higher out of treatment, particularly during the first weeks, and it was elevated during induction onto methadone but not buprenorphine. Mortality during these risky periods changed across time and treatment episodes. Overall, mortality was similarly reduced (compared to out-of-treatment) whether patients were receiving methadone or buprenorphine. It was estimated that the program produced a 29% reduction in mortality across the entire cohort.
Conclusions: Mortality among treatment-seeking opioid-dependent persons is dynamic across time, patient and treatment variables. The comparative reduction in mortality during buprenorphine induction may be offset by the increased risk of longer out-of-treatment time periods. Despite periods of elevated risk, this large-scale provision of pharmacotherapy is estimated to have resulted in significant reductions in mortality.

1. Introduction

Illicit opioid use, especially heroin injection, has caused significant personal and public health problems in many countries across the globe (United Nations Office on Drugs and Crime, 2008). Apart from the burden to users, their families and the broader community, opioid dependence increases the risk of premature mortality (Darke et al., 2006). This elevated risk is concentrated across several causes of death: accidental drug overdose, suicide, trauma (e.g. motor vehicle accidents, homicide or other injuries), and HIV (in countries where HIV is prevalent among people who inject drugs) (Degenhardt et al., 2004, 2006; Darke et al., 2006).

The mainstays of treatment for opioid dependence are pharmacological maintenance on methadone and buprenorphine, both of which are listed on the World Health Organization's (WHO) *Model List of Essential Medicines* (World Health Organization, 2005) for this indication. Methadone is an orally administered opioid agonist with a half-life of 24–36 h. Multiple randomized controlled trials have found that methadone treatment decreases illicit opioid use, improves social functioning, decreases offending behaviors and improves health (Ward et al., 1998; Mattick et al., 2003).

The need for supervised daily dosing of methadone in a defined treatment setting, and evidence of increase overdose death on induction into treatment prompted the search for alternative pharmacological treatment options (Mattick et al., 2001). As a partial agonist, buprenorphine produces less depression of respiration and consciousness than methadone, thereby reducing the overdose risk.

☆ Additional background materials and data analyses are provided in six appendicies available with the online version of this article at doi:xxxxxxxx.

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Buprenorphine is longer acting than methadone, allowing for less than daily dosing.

Opioid pharmacotherapy is not without its own risks (Ward et al., 1998), nor does it completely remove the excess mortality risks that opioid dependent persons are known to face (Darke et al., 2006). Work has shown, for example, high mortality during the period of induction onto methadone (Caplehorn, 1998; Buster et al., 2002). More recent work has found that induction onto methadone, and cessation, carry elevated mortality risks (Caplehorn and Drummer, 1999; Buster et al., 2002; Brugal et al., 2005).

The small sample size of these studies has prevented an assessment of the extent to which these elevated risks are consistent across time and/or patient groups. Few existing examinations have had sufficient power to examine differences in risk across time and patient level variables. Further, these studies have typically focused on treatment groups rather than across entire treatment programs. No estimates exist of the size of reductions in mortality related to treatment for an entire treatment population while also considering other important predictors of mortality risk.

New South Wales (NSW) is the most populous State of Australia, with approximately six million residents. It has had an expanding and expansive opioid replacement program in place for almost thirty years. Over 40,000 people have entered treatment since 1985 (Burns et al., 2009). The size of this entire treatment population allows for an examination of important questions of clinical and population health interest. The aims of this study were to:

(i) Estimate overall mortality for all persons entering opioid pharmacotherapy between 1985 and 2006, by demographic and treatment variables;
(ii) Examine whether demographic or treatment variables were related to mortality levels during and following cessation of treatment;
(iii) Estimate mortality risk, according to specific causes of death, during time within treatment and following cessation of treatment;
(iv) Estimate the number of lives that may have been saved by the provision of methadone and buprenorphine in NSW over this period;
(v) Consider the estimated lives saved from improved clinical delivery of these treatments.

2. Methods

2.1. Sample

The NSW Pharmaceutical Drugs of Addiction System (PHDAS) is a database that records when an authority to dispense methadone or buprenorphine in NSW as an opioid replacement therapy to a particular person has been approved by the NSW Health Department. This study examined unit record data from the PHDAS database on all persons entering pharmacotherapy treatment between 1985 and 2006.

Exclusions from the analysis included: those who did not commence treatment; those in temporary programs, such interstate clients; and buprenorphine clinical trial participants, as they were not necessarily given buprenorphine during the trial.

There were multiple treatment episodes for many individuals and these were sometimes continuous. Previous research using the PHDAS data defined a new treatment episode as one coming 7 or more days after a previous episode had finished. We adopted this definition following consultation with experts in clinical research and practice (Degenhardt et al., 2005). A change in the medication prescribed (methadone or buprenorphine) was considered a continuous episode if there was less than 7 days between one episode end and the next episode start.

We adopted the same definitions – treating the 6 days following a treatment program as part of that program – when allocating deaths to in-treatment or out-of-treatment time periods. There is a potential bias in this methodology to allocate deaths to the treatment period that actually occurred after leaving treatment, but any such errors bias in-treatment mortality *upwards* and out-of-treatment mortality *downwards,* resulting in conservative estimates of mortality reduction during treatment.

All deaths in Australia are coded by expert clinical coders at the Australian Bureau of Statistics (ABS) on the basis of information contained in the death certificate and in some cases from coronial files. For deaths occurring between 1985 and 1996, causes of death were coded according to ICD-9 (World Health Organization, 1977). For deaths occurring between 1997 and 2006, causes of death were coded using ICD-10 codes (World Health Organization, 1993). Only underlying causes were coded in the 1985–1996 period, defined as the "disease or injury which initiated the train of morbid events leading directly to death, or the circumstances of the accident or violence which produced the fatal injury" (Australian Bureau of Statistics, 2007); but up to 19 contributing causes of death were coded from 1997 onwards. Only underlying causes were examined in this study (apart from opioid deaths from 1997 onwards that were cross-classified with particular substance codes). These were grouped into related conditions according to ICD codes based on published expert consensus statements or health department protocols (see Web Appendix 1 and also (Randall et al., 2009) for groupings and sources for definitions).

2.2. Data linkage

Linkage with mortality data from the National Deaths Index was performed by staff at the Australian Institute of Health and Welfare (AIHW) using an in-house probabilistic record linkage program. Variables used for matching purposes included full name, date of birth, sex, date and state of last known contact. A linked data set was forwarded to the investigators on completion of linkage.

2.3. Data analysis

The crude mortality rates (CMRs) were calculated by summing the person-years contributed by each participant, by age, sex, calendar year and treatment time period, summing the numbers of deaths by the same groups, and calculating a rate per 1000 person-years. Crude rate ratios (RRs) were calculated by dividing one mortality rate by another.

Indirect standardized mortality ratios (SMR) were calculated by dividing the observed deaths in the cohort by the expected deaths based on the NSW population mortality rates by year, sex and age group.

In this paper, we have used stratified analyses of SMRs, which allowed us to compare groups, while simultaneously comparing mortality rates against the general population of the same age and sex. We also used Poisson regression to examine predictors of mortality during two time periods: 1985–2000 (methadone only used); and 2001–2006 (methadone and buprenorphine). The results of these regressions have not been included in this paper; the findings were consistent with the results presented in the body of this paper (interested readers can find details of the models at Web Appendix 2). The observed out-of-treatment CMR was applied to the total person-years in the cohort, to provide an estimate of the reductions in mortality resulting from the pharmacotherapy program. This assumes that the mortality reductions were due to treatment. It is nonetheless a conservative estimate because it includes persons who did not die during their first (or subsequent) treatment episode, hence underestimates the mortality rate among untreated opioid dependent persons. Estimated numbers of deaths that might have been averted if the elevated mortality during induction did not exist were made by applying the CMR for the remainder of the treatment period to the total person-years during induction (separately for methadone and buprenorphine). Analyses were conducted in SAS V9.1.3 (SAS Institute Inc., Cary, NC, USA) and Stata V9.2 (StataCorp LP, College Station, TX, USA).

2.4. Ethics

Ethics approval to conduct this study was received from all relevant institutional Human Research Ethics Committees.

3. Results

3.1. Overall results

Over the study period 42,676 clients entered treatment for a total of 425,998 person-years of follow-up (PY; median 9.2 years). The median episode length was 198 days, and participants entered into an average of 2.5 treatment episodes. Further details of treatment retention and re-entry are presented elsewhere (Burns et al., 2009) (see also Web Appendix 3).

During the follow-up period there were 3803 deaths, with an overall CMR of 8.9 deaths per 1000 PY (95% CI: 8.6–9.2; Table 1). CMRs were higher in males than females, and among older clients. The pattern of SMRs was reversed, with a greater excess mortality among females, and a greater excess mortality among younger clients. Mortality rates (both CMRs and SMRs) increased over time until 1995–2000, and fell in 2001–2006 (Table 1, Fig. 1).

The overall in-treatment SMR was 4.5 (95% CI 4.3, 4.8), compared with an out-of-treatment SMR of 8.0 (95% CI 7.7, 8.3). The

Table 1
Crude mortality rates and standardized mortality ratios according to demographic and treatment characteristics among 42,676 NSW opioid pharmacotherapy treatment entrants, 1985–2006.

	Person-years	Total deaths	CMR per 1000 person-years	95% CI	SMR	95% CI
Sex						
Males	276095	2835	10.3	(9.9–10.7)	5.9	(5.7–6.1)
Females	149903	968	6.5	(6.1–6.9)	8.7	(8.1–9.2)
Age group						
Less than 20 years	4735	30	6.3	(4.3–9.0)	12.1	(8.2–17.3)
20–29 years	123143	932	7.6	(7.1–8.1)	8.7	(8.1–9.2)
30–39 years	182329	1486	8.2	(7.7–8.6)	7.3	(7.0–7.7)
40+ years	115791	1355	11.7	(11.1–12.3)	4.8	(4.6–5.1)
Calendar year						
1985–1989	21375	128	6.0	(5.0–7.1)	5.3	(4.4–6.3)
1990–1994	59666	506	8.5	(7.8–9.3)	7.1	(6.5–7.7)
1995–2000	136301	1525	11.2	(10.6–11.8)	8.6	(8.2–9.1)
2001–2006	208656	1644	7.9	(7.5–8.3)	6.2	(5.9–6.5)
Treatment period						
First week in treatment	2178	86	39.5	(31.6–48.8)	35.4	(28.3–43.7)
Second week in treatment	2059	35	17.0	(11.8–23.6)	15.2	(10.6–21.2)
Remainder in treatment	198100	1102	5.6	(5.2–5.9)	4.1	(3.9–4.4)
Overall in treatment	202337	1223	6.0	(5.7–6.4)	4.5	(4.3–4.8)
First week out of treatment	1666	29	17.4	(11.7–25.0)	15.3	(10.2–21.9)
Second week out of treatment	1591	32	20.1	(13.8–28.4)	17.6	(12.0–24.8)
Remainder out of treatment	220404	2519	11.4	(11.0–11.9)	7.9	(7.6–8.2)
Overall out of treatment	223661	2580	11.5	(11.1–12.0)	8.0	(7.7–8.3)
Medication type[1]						
Receiving methadone (1985–2000)	111538	648	5.8	(5.4–6.3)	4.6	(4.2–4.9)
Receiving methadone (starting 2001–2006)	12877	67	5.2	(4.0–6.6)	5.9	(4.5–7.4)
Receiving buprenorphine (starting 2001–2006)	4702	21	4.5	(2.8–6.8)	4.6	(2.8–7.0)
First medication type (2001–2006)						
First given methadone (2001–2006)	21974	148	6.7	(5.7–7.9)	7.3	(6.2–8.6)
First given buprenorphine (2001–2006)	12863	88	6.8	(5.5–8.4)	7.3	(5.8–9.0)
Total	425998	3803	8.9	(8.6–9.2)	6.4	(6.2–6.6)

Person-years do not sum to total as this refers only to time when receiving medications, and 2001–2006 figures are just for those who started treatment 2001 onwards.

rate ratio for the out-of-treatment CMR over the in-treatment CMR showed significantly increased mortality out-of-treatment (RR 1.9, 95% CI 1.8–2.0, $p < .001$). Analysis of mortality by time in treatment revealed that the highest mortality risk was during the first week, with 39.5 deaths per 1000 years of follow up (95% CI 31.6, 48.8), 35.4 times those expected in the general population of the same age and sex (95% CI 28.3, 43.7). Mortality dropped sharply during the second treatment week, and was significantly lower for the remainder of the treatment period compared with the second week (5.6 deaths per 1000 person-years; 95% CI 5.2, 5.9; rate ratio (RR) 0.33, 95% CI 0.23–0.47, $p < .001$). The latter rate was still four times higher than that in the general population (SMR 4.1, 95% CI 3.9, 4.4). Comparison of in-treatment mortality levels among clients entering the program from 2001 onwards prescribed methadone and buprenorphine in the 2001–2006 period revealed no significant differences between the two (RR 0.86, 95% CI, 0.50–1.42, $p = .552$), and there was no difference in the overall SMR for those first given methadone (7.3, 95% CI, 6.2–8.6) in comparison with those first give buprenorphine (7.3, 95% CI, 5.8–9.0) from 2001 to 2006 (Table 1).

3.2. Treatment induction and cessation

A number of interactions existed between treatment variables and mortality risk. The analysis comparing induction on buprenorphine and methadone was restricted to those who entered the program from 2001 onwards. Only one death was estimated to

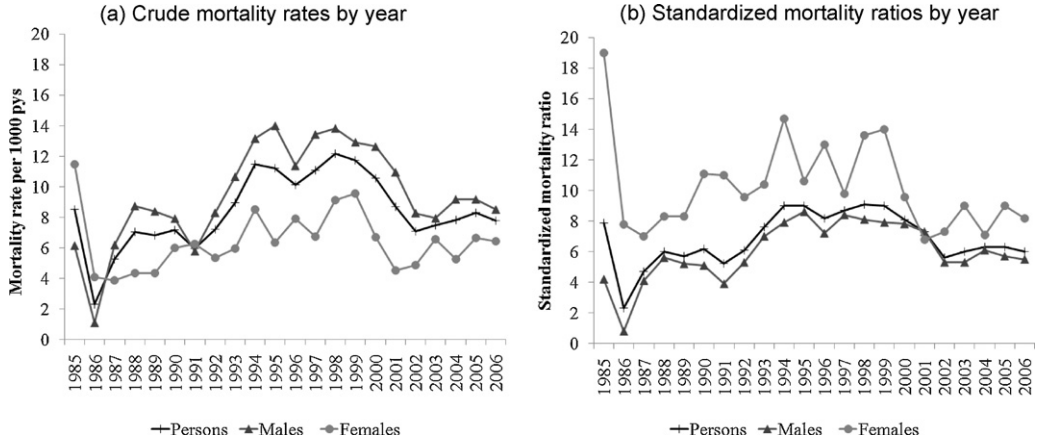

Fig. 1. Mortality levels shown as crude mortality rates per 1000 person-years (*Left Panel*), and standardized mortality ratios (*Right Panel*) among opioid pharmacotherapy entrants in New South Wales, 1985–2006.

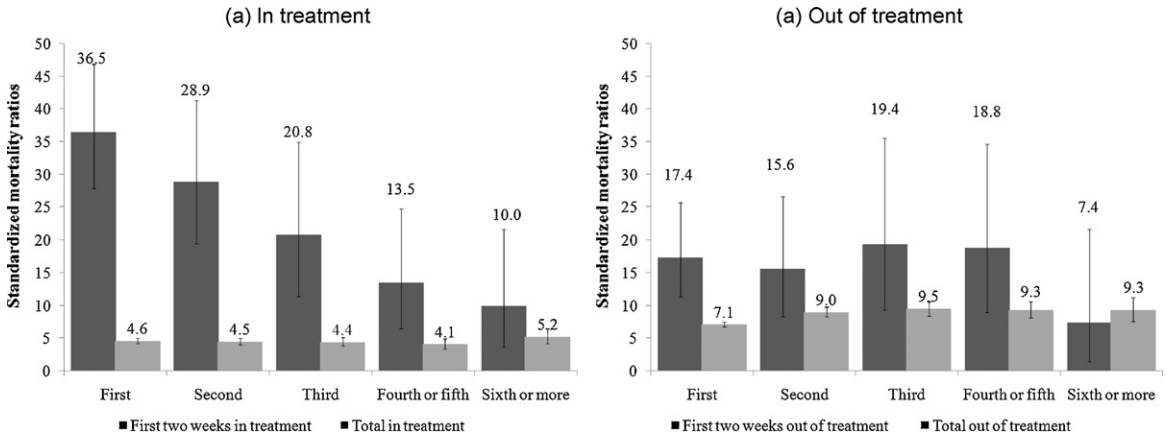

Fig. 2. Interaction between prior treatment and mortality risk (standardized mortality ratios) according to treatment period. In treatment shown in the *Left Panel*; out of treatment shown in the *Right Panel*.

have occurred during induction onto buprenorphine (CMR 2.5; 95% CI: 0.1–13.7); whereas the CMR for those being inducted onto methadone during 2001–2006 was 26.3 per 1000 PY (95% CI: 13.6–45.9) (RR 0.09, 95% CI 0.002–0.63, $p = .004$). The majority of induction deaths occurred in the first two episodes (one out of one for buprenorphine and six out of seven for methadone). No significant differences in mortality risk existed immediately following *cessation* of buprenorphine versus methadone (RR 5.60, 95% CI: 0.63–264.75, $p = .096$) (Web Appendix 4).

The excess mortality seen in the first two weeks of treatment from 1985 to 2006 was strongly related to prior treatment exposure: during the first treatment episode, the SMR during the two week induction period was 36.5 (95% CI 27.9, 46.9), but it decreased with successive episodes to 10.0 (95% CI: 3.7, 21.7; Fig. 2; see also Web Web Appendix 4) for a client entering their sixth (or later) treatment episode. This was a significant trend in the SMRs (RR 0.73, 95% CI: 0.63, 0.84, $p < .001$). Mortality during treatment *overall*, however, was unrelated to prior treatment exposure (RR 1.00, 95% CI: 0.96, 1.04, $p = .971$; Fig. 2a). Mortality in the two weeks following cessation of treatment was no different depending on the number of prior treatment episodes (RR 0.93, 95% CI: 0.77, 1.12, $p = 0.450$; Fig. 2b).

Mortality risk during treatment induction was associated with calendar year (Fig. 3a) with the highest risk in the 1990–1994 period, where the SMR was 52.9 (95% CI: 37.6, 72.3). The excess mortality decreased over time, to 16.5 (95% CI: 10.9, 24.0) in 2001–2006.

Mortality immediately following treatment cessation was consistently elevated across time compared to the general population. *Overall*, the excess mortality was highest for those out of treatment during the 1995–2000 period (Fig. 3b).

3.3. Causes of death

The lower average mortality observed during treatment was found in a limited number of causes of death (Fig. 4a). The in-treatment period was associated with lower mortality from opioid and other drug overdoses, and deaths due to unintentional injury and suicide (Fig. 4a; see also Web Appendix 5). HIV was an uncommon cause of death among the cohort, whether in or out of treatment.

The interaction between treatment period and mortality reflected the effects of specific causes of death. During the first two weeks in treatment, mortality due to opioids and other drugs and unintentional injury and suicide, were all at *much* higher levels than those seen for any other period (in or out of treatment) (Fig. 4b). The mortality risk for these same causes was markedly elevated in the first two weeks out of treatment.

Estimated reduction in mortality among this cohort associated with provision of opioid pharmacotherapy, 1985–2006.

Applying the overall out-of-treatment mortality rate (11.5/1000 PYs) to the total person-years (425,998), it was estimated that 1111 additional deaths would have occurred during the study period if the treatment programme, as implemented, had not existed, an increase in 29% in overall mortality among this group.

Estimates were also made of the number of deaths that might have been averted if the risk during induction (28.6/1000 PYs) was

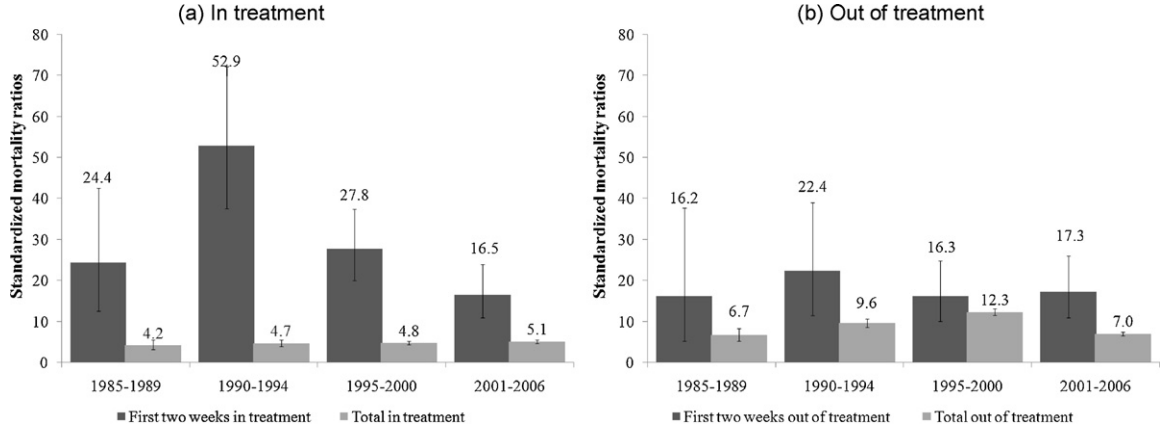

Fig. 3. Interaction between calendar year and mortality risk (standardized mortality ratios) according to treatment period. In treatment shown in the *Left Panel*; out of treatment shown in the *Right Panel*.

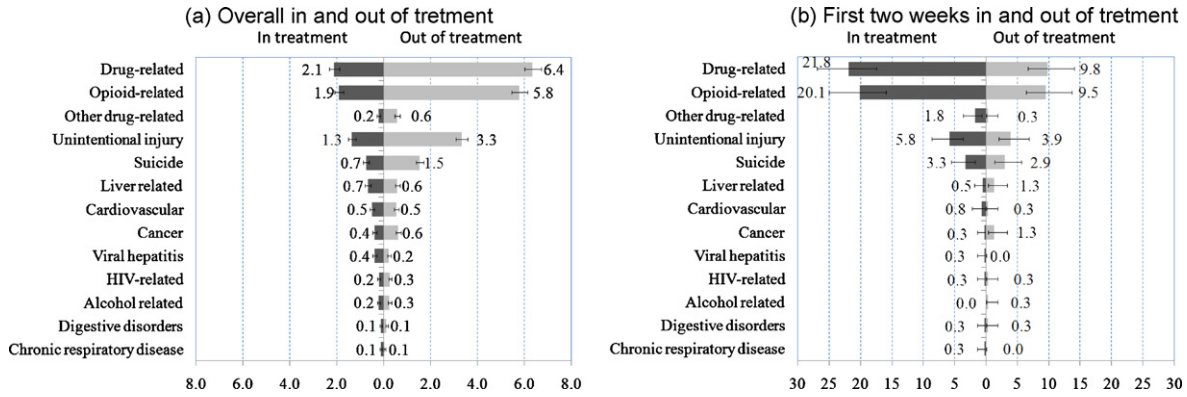

Fig. 4. Crude mortality rates (per 1000 PY) due to specific causes according to treatment period, 1985–2005. Overall in and out of treatment shown in the *Left Panel*; First two weeks in and out of treatment shown in the *Right Panel*.

the same as that during the remainder of treatment (5.6/1000 PYs). With no elevated risk during induction, then 121 deaths observed during induction might have been reduced to 24, 97 fewer deaths across the entire study period.

4. Discussion

This is one of the largest and longest follow up studies of persons receiving opioid pharmacotherapy for illicit opioid dependence. Data were examined on over 40,000 treatment entrants across a large State-based program for whom patterns of entry and departure from treatment were tracked. Time in treatment was associated with lower mortality than time out of treatment, with an overall in-treatment SMR of 4.5 (95% CI 4.3, 4.8), compared to an out-of-treatment SMR of 8.0 (95% CI 7.7, 8.3) (RR 1.9, 95% CI 1.8–2.0, $p < .001$).

The large sample size provided the necessary statistical power to confirm previous observations that induction onto methadone and the first fortnight following cessation of buprenorphine or methadone treatment are particularly risky periods. These elevations in risk varied over time and treatment exposures. Increased prior treatment episodes were associated with *reduced* risk during induction. The calendar period with the highest mortality risk during induction was 1990–1994 consistent with previous findings (Caplehorn, 1998), with later reductions reflecting changes in methadone dosing policies. Post-treatment mortality was highest between 1995 and 2000 when heroin availability and purity were at their historically highest levels in NSW (Degenhardt and Day, 2004; Day et al., 2006). The decline in SMRs during methadone induction with increasing treatment episodes may reflect selection effects, with those at highest risking dying earlier.

The continued elevated mortality risk during induction onto methadone to the end of the study period suggests that despite the adoption of dosing policies to reduce risk, more concerted efforts are needed to minimise these risks.

There are more complex issues for buprenorphine clients. Previous analyses finding they are less likely to be retained in treatment than methadone clients, and more likely to cycle in and out of treatment and switch between medications (Burns et al., 2009). This is of concern given that the period after cessation was equally risky for buprenorphine and methadone clients. The consequence is that any reduction in mortality risk during induction to buprenorphine may be offset by an increased mortality due to longer post-treatment periods. There is a clear need to investigate options to increase retention in buprenorphine treatment, which may include review of dosing levels since inadequate levels have been associated with poorer retention in treatment.

The causes of premature mortality were related to treatment stage. The reductions in risk during treatment were greatest for drug-induced deaths, suicide and traumatic deaths. These are the most common causes of mortality among opioid dependent persons (Darke et al., 2006); they are also fairly directly related to patterns of drug use, poor mental health, and high risk behaviors among those with illicit drug dependence. The fact that HIV mortality was low among this cohort reflects the sustained low prevalence of HIV among people who inject drugs in Australia (National Centre in HIV Epidemiology and Clinical Research, 2007). This, in turn, is linked to the early introduction of Needle and Syringe Programs (NSPs) and the expansion of the methadone program during the mid 1980s when HIV was first identified in Australia. The fluctuations in mortality rate in and out of treatment could also reflect changes in the heroin market in NSW during the period: mortality increased when heroin availability increased during the 1990s, and decreased when supply contracted after 2001 (Degenhardt and Day, 2004; Day et al., 2006).

4.1. Clinical implications

The observed reductions in mortality during treatment, if they can be entirely attributed to treatment, were clinically important and of population health significance. At the population level, the treatment program averted an additional 1111 deaths during the study period. This would have represented a 29% increase in the observed mortality rate.

Despite reductions in the mortality risk in the induction period for methadone from the peak in 1990–1994, the first two weeks of treatment still has an unacceptably elevated mortality risk. Preventive interventions are needed during induction onto methadone, particularly for first-time entrants to treatment. These need to address mental health problems, polydrug use, methadone dose, and lifestyle more generally.

Although buprenorphine did not have the elevated risk in the induction period, the overall treatment mortality levels were not significantly different for those in buprenorphine and methadone treatment. In addition, those who entered buprenorphine were retained for shorter periods, and more likely to cycle in and out of treatment (Burns et al., 2009), leading to more time spent in periods with a higher mortality risk. Overall, those who started in buprenorphine had exactly the same standardized mortality ratio as those who started in methadone, from 2001 onwards. Interventions to increase retention in buprenorphine are also important given the mortality risks faced by those who leave treatment prior to completion.

Interventions are needed to reduce the risks of relapse to drug use and suicide risk at treatment cessation. This is particularly

true among those who have cycled repeatedly in and out of treatment.

4.2. Limitations

In this study, we have compared mortality in- and out-of-treatment. It could be argued that mortality in treatment is lower because the people who stay in treatment are more stable than those who drop out. We doubt that this explains the difference, for three reasons. First, our findings are consistent with evidence from randomised controlled trials finding that opioid substitution treatment reduces mortality (Mattick et al., 2003). Second, in our study all comparisons involve people who chose to enter treatment at some point; we did not compare mortality with dependent users who choose not to seek treatment. We have made no assumptions about mortality reductions compared to opioid-dependent persons who never seek treatment. Third, the elevated causes of mortality during induction and following cessation, were those that opioid maintenance treatment is most likely to affect i.e. those reflecting the risks of a generally more chaotic and dependent illicit drug using lifestyle, such as drug overdose, accidents and suicides.

It is possible that the out of treatment mortality levels we documented are lower than the rates seen prior to treatment entry, or among those who never enter treatment. If this is true, this would reduce the observed difference between in- and out-of-treatment mortality, making our assessment of the mortality reduction in treatment conservative.

5. Conclusions

Mortality among opioid dependent people entering opioid pharmacotherapy is elevated compared to age and sex peers, with overdose, external causes and suicide the major contributors. This elevated mortality is higher when out of treatment (i.e. treatment reduces mortality), and it is particularly elevated during the first weeks out of treatment. The elevation in mortality varied in ways that probably reflect heroin availability and use. Mortality was highest during induction onto methadone. This varied over time, most likely reflecting changing policies on dosing during induction. Finally, this study found that mortality was equivalent whether patients were receiving methadone or buprenorphine. This finding suggests that the comparatively lower mortality during induction for buprenorphine may be offset by the increased risk of mortality during more frequent episodes of treatment entry and cessation that characterise buprenorphine clients.

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Contributors

L. Degenhardt conceived and supervised the study, and led the writing of the article. D.A. Randall undertook the statistical analysis. W.D. Hall contributed to the study design. M. Law provided advice on the statistical analysis of the study. All authors contributed to and have approved the final manuscript.

Conflict of interest

L. Degenhardt has been provided with funding by Reckitt Benckiser in the form of an untied educational grant to monitor the extent of injection of buprenorphine-naloxone injection after its introduction in Australia and to compare this with the injection of other OST forms. The design, conduct and interpretation of that study's findings were the work of the study investigators; Reckitt Benckiser had no role in these.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.drugalcdep.2009.05.021.

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