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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.

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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

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