Exposure to opioid maintenance treatment reduces long-term mortality

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ABSTRACT

Aims  To (i) examine the predictors of mortality in a randomized study of methadone versus buprenorphine maintenance treatment; (ii) compare the survival experience of the randomized subject groups; and (iii) describe the causes of death. Design  Ten-year longitudinal follow-up of mortality among participants in a randomized trial of methadone versus buprenorphine maintenance treatment. Setting  Recruitment through three clinics for a randomized trial of buprenorphine versus methadone maintenance. Participants  A total of 405 heroin-dependent (DSM-IV) participants aged 18 years and above who consented to participate in original study. Measurements  Baseline data from original randomized study; dates and causes of death through data linkage with Births, Deaths and Marriages registries; and longitudinal treatment exposure via State health departments. Predictors of mortality examined through survival analysis. Findings  There was an overall mortality rate of 8.84 deaths per 1000 person-years of follow-up and causes of death were comparable with the literature. Increased exposure to episodes of opioid treatment longer than 7 days reduced the risk of mortality; there was no differential mortality among methadone versus buprenorphine participants. More dependent, heavier users of heroin at baseline had a lower risk of death, and also higher exposure to opioid treatment. Older participants randomized to buprenorphine treatment had significantly improved survival. Aboriginal or Torres Strait Islander participants had a higher risk of death. Conclusions  Increased exposure to opioid maintenance treatment reduces the risk of death in opioid-dependent people. There was no differential reduction between buprenorphine and methadone. Previous studies suggesting differential effects may have been affected by biases in patient selection.

Keywords  Buprenorphine, longitudinal, maintenance treatment, methadone, mortality, opioid dependence, RCT.

INTRODUCTION

Opioid dependence is associated with mortality rates approximately 13 times higher than the general population of the same age and sex [1,2]. Research to date has demonstrated that one of the more effective ways of reducing this increased mortality risk is the provision of opioid replacement therapy which, to date, has been examined for methadone; in one Swedish study, untreated heroin-dependent people had mortality rates 63 times the general population, while the mortality rate was eight times lower in those receiving methadone compared to untreated heroin-dependent people [3]. An Australian study showed that the relative risk of an untreated heroin-dependent person dying was 3.5 times that of a patient receiving methadone maintenance treatment [4]. The diverse predictors of mortality in opioid-dependent subjects have been considered in a number of cohort studies. A London cohort of heroin-dependent participants recruited in 1969 noted that neither the length of heroin use nor the age at study intake predicted survival; however, external factors such as drug market and treatment system changes were associated with mortality rate changes [5]. A Glasgow cohort recruiting 69% of its participants with heroin as the principal drug of choice (11% in methadone treatment) noted that treatment did not have a significant impact on survival; however, the risk of fatality increased through the drug...
user’s career, with younger cohort and human immunodeficiency virus (HIV)-positive cohort members having a more rapidly increasing risk of fatality [6]. A cohort study from Thailand noted that the predictors of mortality in injecting opioid or amphetamine drug users recruited from detoxification treatment included ethnic minority status, incident HIV infection and a longer duration of drug injection [7]. Bisexual sexual orientation, homelessness, infrequent injections of heroin/cocaine ‘speedballs’ and daily use of powdered cocaine or inhalant drugs such as amyl nitrate were all identified as predictors of death in a large group of primarily heroin-using injecting drug users in Washington [8]. These studies have recruited primarily heroin-dependent or injecting drug users from treatment programmes, including methadone maintenance treatment. To our knowledge, none have been noted to recruit from buprenorphine maintenance treatment programmes.

Different maintenance pharmacotherapies may have differential overdose mortality risks: buprenorphine is a partial opioid agonist, whereas methadone is a full opioid agonist [9]. However, there are few published data on mortality associated with buprenorphine treatment compared to methadone, and that which exists is limited to naturalistic studies where patients have self-selected to receive buprenorphine or methadone treatments [10–12], which involves a possible bias in mortality risks between groups. Randomization would remove this selection bias, but no long-term mortality data from randomized studies of methadone versus buprenorphine have yet been published.

Commencing in 1996, a randomized study comparing methadone with buprenorphine maintenance for the treatment of opioid dependence was conducted in Australia [13]. This current study examines the mortality of these 405 randomized study participants 10 years after the commencement of the original study. The study aims to: (i) examine the predictors of mortality in study participants; (ii) compare the survival experience of buprenorphine and methadone-randomized participants, controlled for treatment exposure over time; and (iii) describe the causes of death in the study participants.

METHODS

Participants

Participants consisted of the 405 entrants to a randomized, double-blind trial of buprenorphine versus methadone maintenance therapy for the treatment of opioid dependence, which has been published previously [13]. The participants were recruited originally between 1996 and 1998 from three opioid maintenance treatment clinics in Australia, two in Sydney, NSW and one in Adelaide, South Australia. All were diagnosed as opioid-dependent according to DSM-IV criteria [14], were aged 18 years or older, lived with commuting distance of the clinic and were willing and able to sign informed consent to participate [13]. In the trial, participants were randomized to receive either methadone or buprenorphine for a 3-month (91-day) study period. Participants could then continue to remain on their randomized treatment for an unrestricted time after the study period.

Baseline measures

Self-reported measures used from the original study data included: sex; Aboriginal or Torres Strait Islander origin; highest level of education; employment status; marital status; number of methadone treatment episodes prior to study; and heroin use prior to study (approximate months of heroin use). Sections of the Opiate Treatment Index [15] were used for level of risky injecting practices (including questions on injecting frequency, using a needle used previously by someone else, lending a used needle to others and cleaning used needles for re-use); level of injection-related problems (including questions on drug overdose, tissue damage resulting from injection and difficulty injecting in last month); level of heroin use (‘hits’/sniffing/smokes of heroin per day in last month); and level of polydrug use (number of different drug types used in past month). Dependence severity was measured using the Severity of Dependence Scale [16].

Additional variables completed by study personnel included: completion of study treatment (whether a subject remained in study treatment for the full 91 days or not) and randomized group (either methadone or buprenorphine).

Data included in the study

Mortality data

In 2006, data requests were placed for each of the trial participants to obtain both mortality information and opioid maintenance treatment exposure for the 8–10 years after entry into the original study. To obtain mortality information, full identifying data on the study participants was forwarded to the NSW and SA Births, Deaths and Marriages registries. Identifying data included full name, middle initial/middle name if available, any alias names or alternative spelling (not available for SA participants), date of birth, gender and a date of last known contact (date of randomization to the original study). Searches for matches on the basis of these identified data were conducted by Births, Deaths and Marriages staff. Paper reference copies of NSW death certificates were forwarded to the National Drug and Alcohol Research Centre (NDARC) on 2 February 2006, and
electronic copies of SA death certificates followed some months later. In all analyses, mortality is taken up to the date NSW mortality data were received.

The different primary causes of death were classified into a number of categories: drug overdose, trauma (e.g. gunshot, hanging, injuries), cancer, HIV/AIDS or its complications, other medical complications, or hepatitis or its complications.

**Treatment exposure**

Treatment data for both states were obtained by a request to the bodies administering methadone and buprenorphine treatment: the Pharmaceutical Services Branch, NSW Health and Drug and Alcohol Services South Australia. For all methadone and buprenorphine treatment episodes undertaken by study participants since randomization to the original study, episode start and end dates, type of treatment, and information on the medication dosing point were requested. This information was obtained through database search by patient name and identifier number in NSW and via hand-searching of clinical records by name in SA and forwarded electronically to NDARC.

Treatment data were then sorted into discrete ‘episodes’ of treatment, where a new episode commenced if the subject entered opioid maintenance treatment more than 7 days after exiting prior treatment, or if the subject changed between methadone and buprenorphine maintenance treatments. In cases where the subject’s prescribing doctor or dosing location changed without there being a 7-day interval between exiting and re-entering treatment, this was considered to be a continuous episode of treatment. Episodes of treatment were coded either as methadone treatment longer than 14 days, buprenorphine treatment longer than 14 days and/or opioid (methadone or buprenorphine) maintenance treatment longer than 7 days. The first 14 days of treatment is generally considered to be the highest risk time of methadone maintenance treatment [17], and this same period of time was also applied to buprenorphine treatment for consistency. The cut-off period of 7 days was selected as this is the approximate duration of physical heroin withdrawal symptoms [18] and the length of several commonly used out-patient heroin withdrawal regimens in use in Australia [19,20]. It should be noted that exposure to buprenorphine treatment was anticipated to be less than methadone treatment, because buprenorphine treatment became more accessible only gradually in Australia after its registration in 2000 and subsidization through the Pharmaceutical Benefits Scheme from 2001 [21]. However, all participants randomized originally to buprenorphine treatment were permitted to remain in this treatment until the drug was registered officially.

**Statistical analyses**

Analyses were conducted using SAS version 9.1 and Excel 2003. Initial tests included basic descriptive analysis, t-tests and χ² tests. In survival analysis, log-rank tests were used and participants still alive at the analysis point (2 February 2006) were censored. For survival regression models, possible predictors of mortality were identified through literature searches and obtained through the study baseline interview data and the longitudinal data of treatment exposure.

Predictors of mortality were investigated using proportional hazards survival analysis models. Those variables with log-rank P-values less than 0.25 in univariate regressions, the original randomized study group variable, and all interaction terms between the variables were retained for consideration in the proportional hazards survival model. Backwards stepwise elimination was used, commencing with the least significant interaction terms and progressing to the main effects. Variables with Wald P-values of less than 0.05 were retained in the model. If an interaction term was retained, the two main effects for which the interaction was being considered were also retained in the model. The final model was then examined for possible violations of the proportional hazards assumption.

Ethics approval to conduct the present mortality study was received from UNSW Human Research Ethics Committee and the Royal Adelaide Hospital Ethics Committee.

**RESULTS**

**Sample characteristics**

A total of 200 participants were randomized to buprenorphine and 205 participants to methadone. The sample was 69% male, median 28 years of age (18–58 years). Five per cent classified themselves as of Aboriginal or Torres Strait Islander (ATSI) origin, 50% had completed 9–10 years of education and 66% were unemployed at study entry. At baseline, participants were using a median of 2.6 ‘hits’ or ‘shots’ of heroin per day, and had used a median of four different drug categories in the month before study entry. There were no significant differences between the randomized groups in demographics or drug use variables [13].

**Treatment exposure in the follow-up period**

Fifty-three per cent of participants remained in treatment for the full 3 months of randomized study treatment. The follow-up period included the period of randomized treatment until the mortality data extraction on 2 February 2006, and amounted to 3394 person-years. There was no difference over the follow-up period in percentage time
exposure to opioid maintenance treatment episodes greater than 7 days ($t = 0.64, P = 0.52$) across randomized groups. Participants spent a median of 43% of follow-up time in episodes of maintenance treatment lasting longer than 7 days, across a median of two episodes.

Significant differences were noted in the exposure to methadone and buprenorphine between the randomized treatment groups. Participants randomized to methadone treatment were significantly more likely to spend greater percentage follow-up time in methadone treatment episodes longer than 14 days ($t = 4.83, P < 0.0001$), and participants randomized to buprenorphine were similarly significantly more likely to spend longer time in buprenorphine treatment episodes longer than 14 days ($Z = 11.45, P < 0.0001$).

### Mortality

There were 30 deaths in the follow-up period (16 in the buprenorphine randomized group, 14 in the methadone randomized group), with an overall mortality rate of 8.84 deaths per 1000 person-years of follow-up.

Twenty-seven deaths definitely occurred while participants were not registered in opioid maintenance pharmacotherapy—a mortality rate of 14.29 deaths per 1000 person-years while 'out of treatment'. Three deaths occurred while a pharmacotherapy treatment episode was still officially 'open' (1.99 deaths per 1000 person-years), but in two of these cases we considered their actual treatment status at death uncertain: one subject died of complications of opioid toxicity over a year before their episode of buprenorphine treatment was officially completed, while the second died from cancer approximately 3 years before their episode of methadone treatment was officially terminated. The final fatal case in an open episode of treatment died from multi-drug toxicity 555 days after commencing methadone. If we assume that this was the only death 'during treatment', the mortality rate is 0.66 per 1000 person-years.

There was a median of almost a year (355 days) between the completion of an opioid maintenance treatment episode and death. One death (by gunshot wound) occurred 3 days after treatment completion; no other deaths occurred within a fortnight of treatment completion. One death (by heroin toxicity) occurred during naltrexone treatment for opioid withdrawal.

### Predictors of mortality during follow-up

The following variables were excluded at the univariate stage on the results of log-rank tests ($P > 0.25$): sex, highest level of education, baseline employment status, baseline marital status, months of heroin use prior to study, level of polydrug use, level of risky injecting practices, level of injection-related problems, whether subject completed initial study treatment (91 days) and number of methadone treatment episodes prior to study entry.

The regression model initially included eight main effects and 28 associated interaction terms. Backwards stepwise regression was used, allowing for missing values. The percentage time spent in opioid treatment greater than 7 days and both the percentage time and number of treatment episodes for more than 14 day methadone and buprenorphine treatment were excluded during the modelling process for $P \geq 0.05$. The final model showed no major violations of the proportional hazards assumption. Table 1 shows all those variables included in the final model.

Controlling for all other factors in the model, exposure to every additional treatment episode of methadone or buprenorphine treatment lasting longer than 7 days, reduced the risk of death on average by 28% [95% confidence interval (CI) 7–44%]. Participants identifying as

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**Table 1** Predictors of mortality, adjusted multivariate statistics.

<table>
<thead>
<tr>
<th>Variable description</th>
<th>Test statistic</th>
<th>$P$-value</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>2.32</td>
<td>0.13</td>
<td>NR</td>
</tr>
<tr>
<td>ATSI origin (yes or no)</td>
<td>7.20</td>
<td>0.0073</td>
<td>5.32 (1.89, 14.95)</td>
</tr>
<tr>
<td>Dependence severity (score/15)</td>
<td>6.86</td>
<td>0.0088</td>
<td>NR</td>
</tr>
<tr>
<td>Level of heroin use (uses/day)</td>
<td>9.05</td>
<td>0.0026</td>
<td>NR</td>
</tr>
<tr>
<td>Randomized group (MMT or Bup)</td>
<td>6.19</td>
<td>0.013</td>
<td>NR</td>
</tr>
<tr>
<td>No. of opioid treatment episodes</td>
<td>7.60</td>
<td>0.0058</td>
<td>0.72 (0.56, 0.93)</td>
</tr>
</tbody>
</table>

*Interaction terms between all variables were considered, but for brevity only those remaining in the final model have been reported here. Hazard ratios (HR) have not been reported for the individual variables that make up significant interaction terms in the model, although these individual variables remained in the model. LR = likelihood ratio, NR = not reported, MMT = methadone maintenance treatment, Bup buprenorphine.
Aboriginal or Torres Strait Islander origin had 5.32 times the risk of death of non-Aboriginal or Torres Strait Islander participants, controlling for other model factors (95% CI 1.89–14.95).

Interestingly, among more dependent participants using more heroin at baseline, the risk of death during follow-up was 12% lower (95% CI: 5–18%) than less dependent, less frequent heroin users at baseline. Post hoc exploratory analyses suggested that this might have been related to more dependent and heavier heroin users being more likely to spend more time in opioid maintenance treatment. Participants with the top 50% of dependence severity and the top 50% of heroin use at baseline spent significantly more time in opioid maintenance treatment longer than 7 days, compared to those participants in the lower 50% of both categories (median 54.36% versus 37.13% of follow-up, t = 2.17, P = 0.031).

Among older participants randomized to buprenorphine treatment at treatment entry, the risk of death during the follow-up period was 11% lower (95% CI: 2–19%) than younger participants who were randomized to methadone at study entry. Post hoc analyses of this association suggested that this could have been related to the time spent in buprenorphine treatment. Older participants randomized to buprenorphine treatment spent significantly more time in buprenorphine treatment longer than 14 days (median 7.17% versus 0% of follow-up, Z = 8.45, P < 0.0001), and significantly less time in methadone treatment longer than 14 days (median 8.81% versus 29.50% of follow-up, t = 2.05, P = 0.042) compared to younger participants randomized to methadone treatment. These subject groups did not significantly differ on the time spent in either opioid maintenance treatment longer than 7 days (median 45.85% versus 33.30% of follow-up, t = 1.43, P = 0.16).

**Causes of death**

Drug overdose or related complications were the most common cause of death in the 30 deceased participants, accounting for 40% of the deaths. Causes of death and mortality rates are presented in Table 2.

<table>
<thead>
<tr>
<th>Table 2 Causes of death.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cause of death</td>
</tr>
<tr>
<td>__________________________</td>
</tr>
<tr>
<td>Drug overdose or its sequelae</td>
</tr>
<tr>
<td>Trauma (e.g. gunshot wounds, hanging, asphyxia)</td>
</tr>
<tr>
<td>Other medical reasons (e.g. hepatic encephalopathy, endocarditis)</td>
</tr>
<tr>
<td>Cancer</td>
</tr>
<tr>
<td>AIDS or its complications</td>
</tr>
<tr>
<td>Cause of death unknown</td>
</tr>
<tr>
<td><strong>Total</strong></td>
</tr>
</tbody>
</table>

+py = person-years.

more likely to die than non-Aboriginal or Torres Strait Islander participants. Indigenous status remains a well-recognized mortality risk in Australia [26].

Two significant interaction terms in our regression model showed some interesting effects. More severely dependent, heavier heroin-using participants were less likely to be dead at follow-up. This unexpected finding could be explained partially by these participants spending more time in stable maintenance treatment episodes and thus reducing their mortality risk. Indeed, more dependent, heavier heroin-using participants at baseline spent significantly more study follow-up time in opioid maintenance treatment longer than 7 days, compared to less dependent, less heroin-using participants (t = 2.17, P = 0.031). This is a promising finding, implying that, at least in the NSW and South Australian clinical settings, those people who have the greatest need of opioid maintenance treatment are able to access it; and by so doing, they reduce their mortality risk.

Older participants randomized to buprenorphine treatment were less likely to be dead at follow-up. While older participants randomized to buprenorphine treatment spent significantly more time in buprenorphine maintenance treatment longer than 14 days (Z = 8.45, P < 0.0001), they did not spend significantly more time in opioid maintenance treatment longer than 7 days, compared to younger participants randomized to methadone treatment. It appears that the older people randomized to buprenorphine may have benefitted more in terms of their survival from exposure to buprenorphine rather than exposure to methadone treatment. Further research is needed to clarify this.

It has been questioned whether methadone and buprenorphine maintenance treatment had different long-term mortality outcomes, but so far this question...
has been addressed only in self-selected treatment samples [10,11]. Previous studies did not allow for direct control for characteristics of the respective treatment populations, which probably differed in other important ways that impact upon mortality risk. This is the first study that has examined mortality risk in a randomized controlled trial of these two pharmacotherapies. In this randomized study we can see that the original study randomization had no direct impact on long-term mortality, except in the case of older participants randomized to buprenorphine treatment, who showed improved survival.

Seven per cent of participants died during follow-up, giving a crude mortality rate of 8.84 deaths per 1000 person-years of follow-up. Only one death occurred during opioid maintenance treatment (methadone) and an additional death occurred during naltrexone withdrawal treatment. Deaths were predominantly from opioid overdose or trauma, consistent with the literature [27], and the mortality rates for these causes of death were comparable to rates reported previously [28]. The low AIDS-related mortality is a clear reflection of the low prevalence of HIV in the Australian injecting drug user population [29]. While the impact of the high hepatitis C prevalence in Australian opioid-dependent was not reflected in the primary causes of death, it and other comorbid conditions have been shown to be a significant source of morbidity in this population [30,31] and may have contributed to some of the deaths.

Limitations

The primary limitation of this study concerns the ease of availability of buprenorphine treatment exposure over time, as the original study was commenced prior to buprenorphine treatment registration in Australia. The ideal situation to examine the impact of methadone and buprenorphine on mortality would be in a long-term randomized study where patients had ready access to their randomized treatment over time but were not permitted to change between treatments. As this is clearly not feasible, the current study design would seem to be the next best option. As there were no significant differences between study groups at baseline, we were able to control for patient characteristics in our analyses, and found no differential effect of the time that was spent in buprenorphine versus methadone treatment.

Treatment exposure other than opioid maintenance pharmacotherapies such as naltrexone was not measured routinely. It is possible that exposure to other treatments had an impact on mortality, but as methadone and buprenorphine account for the great majority of opioid dependence treatment in Australia we expect this effect to be a minor one.

CONCLUSIONS

This study examined mortality risk in a randomized controlled trial of methadone versus buprenorphine maintenance treatment. Exposure to episodes of opioid maintenance treatment reduces mortality in opioid-dependent participants, and there did not appear to be a differential effect of methadone or buprenorphine exposure on mortality. Only one death occurred during an opioid maintenance treatment episode. Interestingly, more dependent, heavier heroin users had a reduction in mortality risk associated with greater exposure to opioid maintenance treatment than less heavy or dependent users; further, older participants randomized to buprenorphine treatment had significantly improved survival, perhaps from an increased exposure to buprenorphine treatment. Causes of death were consistent with those reported previously in the literature. While exposure to methadone and buprenorphine treatment after the conclusion of the randomized controlled trial were influenced by the availability of treatments over time, we have demonstrated that greater access to opioid maintenance treatment episodes, whether buprenorphine or methadone, reduces mortality risk in opioid-dependent people.

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