Examination of mortality rates in a retrospective cohort of patients treated with oral or implant naltrexone for problematic opiate use

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ABSTRACT

Aims To examine and compare mortality rates in patients treated with oral and implant naltrexone. Design A retrospective cohort study. Setting A community not-for-profit drug treatment clinic. Participants Patients treated with oral naltrexone (n = 2155, 17,207 patient-years) and implant naltrexone (n = 2389, 11,678 patient-years) for problematic opiate use between August 1997 and December 2009. Measurements Crude gender, age, treatment period and cause-specific mortality rates were calculated using data obtained from the National Death Index. Findings Crude mortality rates for patients treated with oral naltrexone [8.78 deaths per 1000 patient-years (ptpy), 95% confidence interval (CI): 7.38–10.17] were significantly different to those treated with implant naltrexone (6.59 ptpy, 95% CI: 5.13–8.06) (P = 0.0339). During the first 4 months following treatment, differences in the two groups were particularly apparent, with a mortality rate of 26.28 ptpy in patients treated with oral naltrexone compared to 7.34 ptpy in patients treated with implant naltrexone (P = 0.0003). Differences in initial mortality rates following treatment were associated predominantly with high rates of opiate overdoses in oral naltrexone patients during the first 4 months following treatment (17.22 ptpy compared with 0.67 ptpy in implant naltrexone patients) (P < 0.0001). Conclusions The use of implant naltrexone can reduce all-cause mortality and opiate overdose during the first 4 months following treatment compared with patients treated with oral naltrexone.

Keywords Naltrexone, mortality, opiates, overdose death.

INTRODUCTION

Since its initial US registration in 1984 for the treatment of opiate dependence, a number of safety concerns have been raised regarding the use of oral naltrexone [1]. These are: (i) an observed increase in the number of opiate overdoses following cessation of oral naltrexone [2,3]; (ii) the potential for increased use of non-opiate drugs resulting in increases in fatal and non-fatal non-opiate drug overdoses [4,5]; and (iii) increases in depression and suicide due possibly to the inability of endogenous opiates to bind to the opiate receptor [1,6].

Mortality rates for heroin-using populations have been estimated at between 6.8 and 77.6 per 1000 patient-years (ptpy), with clear geographical differences in mortality [7]. Mortality rates in Australia are among the lowest in the world, with crude mortality rates of between 8.9 and 18.0 [7]. Patients in methadone maintenance therapy (MMT) and buprenorphine maintenance have mortality rates generally between 4.5 and 15.2 ptpy [8–10]. Mortality rates for oral naltrexone remain comparable to other drug treatments (approximately 10 ptpy); however, mortality rates have been calculated to be as high as 221 ptpy in the 2 weeks following cessation of oral treatment [3,11].

The observed increase in opiate fatalities following the cessation of oral naltrexone is postulated to be associated with a reduction in a patient’s opiate tolerance as patients transition from regular opiate use to naltrexone [3,12,13]. While taking daily naltrexone, patients are
protected from opiate overdose; however, once the naltrexone is not present, low opiate tolerance can result in opiate dose miscalculation and accidental overdoses [3].

Recently a number of sustained-release naltrexone products have been developed to overcome patient non-compliance with daily oral naltrexone use and provide stable therapeutic blood naltrexone levels over an elongated time-period [14]. The development of sustained-release naltrexone preparations has also been associated with safety concerns. As per oral naltrexone, issues have centred on the perceived potential for increases in fatal and non-fatal opiate and non-opiate drug overdoses following treatment, as well as potential increases in the prevalence of depression and suicide [15,16]. These concerns received increased attention recently following the registration of the first sustained-release naltrexone preparation for the treatment of opiate dependence by the Food and Drug Administration (FDA) in the United States [17,18]. The preparation, known as Vivitrol® is a 30-day sustained-release injection, manufactured by Alkemes (Waltham MA, USA). Despite receiving FDA approval and having been registered for alcohol dependence since 2006, the lack of data available on the presence of fatal and non-fatal opiate overdoses has been criticized [17,18].

Similar concerns have surrounded the use of the O’Neill Long Acting Naltrexone Implant (OLANI), developed and produced in Australia by Go Medical Industries Pty Ltd (Perth, Australia) [15,19]. In contrast to the injectable formulation, this implantable treatment is placed surgically into the subcutaneous tissue, producing blood naltrexone levels above therapeutic levels of 2 ng/ml for approximately 145 days, decreasing gradually to 1 ng/ml by 214 days [20]. This preparation has also been shown to be superior to oral naltrexone in preventing return to regular heroin use in the 6 months following treatment [21].

A review of Australian coronial records between 2001 and 2004 identified five drug-related fatalities in patients treated with implant naltrexone, suggesting that the patients treated with implant naltrexone were not protected from overdose. Notably, however, the study identified only one fatality involving opiates in a patient with an implant less than 6 months old (which is the outer duration of the longest implant available in Australia), and the manufacturer of the implant was not identifiable [15].

Notwithstanding this, a study of 361 heroin-dependent patients treated with the Go Medical implant observed a reduction in rates of non-fatal opiate overdoses requiring hospital admission from 5.5% in the 6 months prior to treatment to 0% during the first 6 months following treatment and 0.8% in the subsequent 6 months [22]. It was hypothesized that the implant’s slowly tapering release profile reduced fatal and non-fatal overdoses not only in the therapeutic period post-treatment, but also the post-therapeutic period, where low levels of naltrexone have been demonstrated up to 12+ months post-treatment [20,22].

Comparisons of mortality rates in heroin-dependent people treated with the Go Medical implant have found mortality rates to be comparable to both methadone (5.83 ptpy for methadone compared with 3.76 ptpy for implant naltrexone) [23] and buprenorphine (5.35 ptpy for buprenorphine compared with 3.00 ptpy for implant naltrexone) [24]. The sample size used in the naltrexone cohort in each of these studies was relatively small (341 and 255 patients, respectively), limiting the ability to assess change accurately in mortality rates over time and the frequency of fatal opiate overdoses. It may therefore be hypothesized that the rate of opiate overdoses may be reduced in patients treated with implant naltrexone compared with patients treated with oral naltrexone.

The current study examined crude mortality rates in a large cohort of opiate-dependent people treated with oral or implant naltrexone. Additionally, the study focused on deaths attributable to opiate and non-opiate drug mortality and suicide to determine whether or not there was evidence of an increase of all-cause subgroup mortality in patients treated with implant compared with oral naltrexone.

**METHODS**

**Subjects**

The study cohort consisted of 1467 patients treated with oral naltrexone, 1701 patients treated with implant naltrexone (OLANI) and 688 patients treated with both at a community not-for-profit drug treatment clinic, between August 1997 and December 2009. Patients included in the cohort were treated for problematic opiate use (most commonly heroin dependence) defined by self- and clinically identified problems controlling the patient’s opiate usage. Patients treated were predominantly male (61.25% oral and 62.87% implant), aged between 25 and 35 years at the time of first treatment (27.24 ± 6.89 years for oral and 30.5 ± 7.71 years for implant) and between 30 and 40 years of age at the conclusion of the study (37.07 ± 6.99 years for oral and 35.41 ± 7.60 years for implant).

Patients were treated with oral naltrexone (prior to its registration in Australian in 2000) and implant naltrexone under the Therapeutic Goods Administration’s (TGA) Special Access Scheme, which allows a physician to use a non-registered pharmaceutical product on a named-patient basis to patients at an increased risk of morbidity or mortality. At present, implant naltrexone is only used
routinely at a single clinic in Perth, Western Australia (WA) (the site examined in this study). While the site treats primarily WA patients, approximately 20% of all patients treated with implant come from interstate. Patients treated with oral naltrexone after 2000, following the registration of oral naltrexone in Australia, were prescribed oral naltrexone by a clinic physician.

In this study, an oral naltrexone treatment was defined as induction onto oral naltrexone. In the majority of cases, induction took place after rapid opiate detoxification (as described in [25]). An implant naltrexone treatment was defined as the surgical insertion of a naltrexone implant/s (generally one to three implants). The implant composition and standard procedure used for the treatment of patients with this implant preparation have been described previously [26].

Data linkage

Data from the two cohorts were submitted to the Australian Institute of Health and Welfare (AIHW) as a password-protected document. The document contained the patient’s study ID, first given name, second given name, third given name, surname, gender, date of birth, date of last treatment, last known state of residence and the date of death (if known to be dead). Where patients were known by multiple names, multiple records were created for each known alias. Prior to submission, the two databases used to compile the data were cross-matched to detect abnormalities.

Once submitted to the AIHW, the patient database was cross-referenced against the National Death Index (NDI), which lists all deaths occurring in Australia since 1980. Additionally, the database contains information on the death of Australians that occurred overseas, on the provision that the deaths are reported to the Australian Embassy of the country in which the death occurred. Data-matching was undertaken by AIHW staff using the Integrity probabilistic matching software. For each potential match a weighting was assigned estimating the likelihood of an accurate match. All potential matches were then checked manually. Matches with small discrepancies were re-checked against the patient’s file. Data provided by the AIHW included patient names, sex, date of birth, date of death, state registering the death, year of death registration, underlying cause of death and other causes of death. Cause of death (COD) was expressed as an ICD-10 code.

Subjects identified on the NDI registry who had died in Western Australia, but had not been assigned a COD, were submitted to the Western Australia Registry of Births, Deaths and Marriages. COD was provided from the Registry as a single-sentence summary. Clarification was sought for any ambiguous COD through the Coroner’s Court; for example, to determine if an ‘acute combined respiratory drug effect’ involved the use of opiate or non-opiate drugs.

Data analysis

Crude mortality rates were calculated using two approaches: initial treatment and all treatments, based on the separation of the patients into oral and implant naltrexone treatment groups. The initial treatment approach separated patients into oral and implant naltrexone-treated patients based on their first naltrexone treatment. For patients who moved onto the alternative treatment later (i.e. changed from oral to implant), data collected after the new treatment were no longer included. In the all-treatment approach, patients were separated into oral and implant naltrexone treatment groups; patients treated with both therapies were included in both treatment groups. Using this method, the number of patient-years attributed to each group was calculated from the commencement of a treatment to the commencement of the alternative treatment, with fatality assigned to the most recent treatment.

Additionally, age-specific, age-standardized, gender-specific and cause-specific mortality rates were calculated for patients in the oral and implant naltrexone treatment groups using the all-treatment approach (with the exception of gender, which was carried out using both methods). Age-standardized mortality rates (ASM) were calculated using data obtained from the Australian Bureau of Statistics (ABS) on the age demographic of Australians aged between 18 and 75 years in June 2009 [27]. Cause-specific mortality was examined for deaths associated with the three main causes of interest: opiate poisoning (T40.0–T40.4/T40.6/X42/X62/Y12), non-opiate poisoning (T40.5/T40.7–T40.9/T41.2/T42.3–T42.7/T43.0–T43.2/T43.6/T43.8/T51–T53/T59.0/ T59.8/T59.9/T65.2/T65.3/T65.6/X41/X44/X45/X46/ X49/X61/X65/X66/X69/Y11/Y14/Y15/Y16/Y19) and suicide/self-harm (X60–X84/X87.0), using ICD-10 codes assigned to the fatalities.

Mortality rates were also calculated in terms of time following treatment. For the first 12 months following treatment, mortality rates were examined for 4 monthly periods. Following this, yearly periods were examined for 1–5 years and then for greater than 5 years for both treatment groups. The time following treatment was calculated as the period from the treatment date to the next treatment event or the end of the study if there was no subsequent event.

Confidence intervals (95% CI) were calculated for each of the mortality rates. A two-tailed Z-test was used to compare mortality rates. A P-critical value of 0.05 was
For patients in whom the date of death was unascertainable, the mid-point of the range given on the death certificate was used.

**Ethics**

This study protocol was reviewed and approved by Bellberry Human Research Ethics Committee (A148/08), and the AIHW Ethics Committee (EC 2010/1/7). Reciprocal approval was also ascertained from the University of Western Australia Human Research Ethics Committee (RA/4/1/4043).

**RESULTS**

Oral patients ($n = 2155$) were followed for a total of 17,207 patient-years, in which 3768 oral treatments were delivered, with an average of 1.75 treatments per oral patient. The implant patients ($n = 2389$) were followed for 11,678 patient-years and treated with 4724 implant treatments, with an average of 1.97 treatments per implant patient. Oral patients were followed-up for an average of 7.98 years, while implant patients were followed-up for an average of 4.88 years.

**Crude mortality**

For the 3856 patients submitted to the AIHW, 228 fatalities were identified in the NDI following manual checking of the matches. Seventy-seven deaths were attributed to the implant naltrexone group and 151 to the oral naltrexone group. Mortality rates in patients whose first treatment was oral naltrexone were not significantly different to patients who were first treated with implant naltrexone ($P = 0.1117$); however, using all treatments there was a significant difference ($P = 0.0339$) with mortality rates of 8.78 ptpy (95% CI: 7.38–10.17) for oral naltrexone patients and 6.59 ptpy (95% CI: 5.13–8.06) for implant naltrexone patients (Table 1).

**Gender- and age-specific mortality**

In patients treated with oral naltrexone, no significant difference was observed in gender-specific mortality rates. However, females treated with implant naltrexone had a significantly lower mortality rate than males treated with the implant ($P = 0.0010$) (Table 2). A significant difference was observed in the youngest of the five age-brackets ($P = 0.0135$); however, there was no difference in the remainder. Age-standardized mortality rates accentuated differences in crude mortality rates, with 26.78 ptpy for oral patients (24.37–29.19) and 13.77 ptpy of implant patients (11.66–15.88).

**Time following treatment**

During the first 4 months following treatment, mortality rates in oral naltrexone-treated patients were significantly higher than in patients treated with implant naltrexone (26.28 ptpy in oral compared with 7.34 ptpy in implant groups, $P = 0.0003$). In subsequent time-periods there was only a significant difference between the treatments in 8–12 months ($P = 0.0010$) (Fig. 1).

**Cause morbidity**

Of the 228 fatalities recorded, 206 (90.4%) had a recorded cause of death, equating to 0.64 ptpys for the oral group and 1.03 ptpy for the implant group. Overdoses involving opiates, overdoses involving non-opiate drugs and suicide were the three most common causes of death (Table 3). No significant difference was noted between the two groups in the rate of each of the causes.

The large increase in mortality observed during the first 4 months following treatment with oral naltrexone

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**Table 1** Crude and gender-specific mortality rates for patients treated with oral or implant naltrexone.

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral initial</td>
<td>8.92 (7.50–10.33)</td>
<td>9.84 (7.94–11.74)</td>
<td>7.46 (5.38–9.54)*</td>
</tr>
<tr>
<td>Implant initial</td>
<td>7.00 (5.10–8.89)</td>
<td>8.58 (5.93–11.23)*</td>
<td>4.32 (1.88–6.75)*</td>
</tr>
<tr>
<td>Oral all</td>
<td>8.78 (7.38–10.17)*</td>
<td>9.69 (7.82–11.56)</td>
<td>7.34 (5.29–9.38)*</td>
</tr>
<tr>
<td>Implant all</td>
<td>6.59 (5.13–8.06)*</td>
<td>8.40 (6.41–10.42)*</td>
<td>3.75 (1.97–5.53)*</td>
</tr>
</tbody>
</table>

*Significant difference ($P < 0.05$).

**Table 2** Age-specific mortality rates in patients treated with oral or implant naltrexone, expressed per 1000 patient-years.

<table>
<thead>
<tr>
<th></th>
<th>Oral</th>
<th>Implant</th>
</tr>
</thead>
<tbody>
<tr>
<td>18 ≥ age &gt; 25</td>
<td>10.27 (6.61–13.92)*</td>
<td>4.22 (1.10–7.33)*</td>
</tr>
<tr>
<td>25 ≥ age &gt; 35</td>
<td>7.74 (5.93–9.54)</td>
<td>6.92 (4.86–8.98)</td>
</tr>
<tr>
<td>35 ≥ age &gt; 45</td>
<td>9.08 (6.20–11.95)</td>
<td>5.79 (2.96–8.62)</td>
</tr>
<tr>
<td>45 ≥ age &gt; 55</td>
<td>9.01 (3.15–14.87)</td>
<td>8.40 (2.60–14.19)</td>
</tr>
<tr>
<td>≥ 56</td>
<td>77.68 (4.57–150.80)</td>
<td>34.60 (3.87–73.07)</td>
</tr>
</tbody>
</table>

*Significant difference ($P < 0.05$).
was due primarily to very high levels of opiate overdose fatalities, with rates of overdose death 25 times that observed in the implant treatment group for the same period (17.22 ptpy for oral compared with 0.67 ptpy for implant patients) \( (P < 0.0001) \). The statistical difference in opiate overdose mortality was apparent for the first 12 months following treatment, after which the difference was no longer apparent (Fig. 2).

Notably, in young patients (18–25 years), mortality associated with opiate overdose made up half the total mortality rate in patients treated with oral naltrexone (5.13 ptpy), far greater than any of the other age brackets. In contrast, no mortality was associated with opiate overdose in young patients treated with implant naltrexone. A single opiate fatality was detected within the first 4 months following treatment with implant naltrexone. The coroner’s report provided a primary diagnosis of acute opiate toxicity, with blood morphine levels of 16 ng/ml (total) and 13 ng/ml (free) (a ratio of 1.23 indicating a rapid overdose [28]). Diazepam (0.7 ng/ml), desmethyldiazepan (0.9 ng/ml), temazepam (0.03 ng/ml), oxazepam (0.06 ng/ml), tetrahydrocannabinol (0.9 ng/ml) and carboxytetrahydrocannabinol (95 ug/l) were found. Trace amounts of methamphetamines and amphetamines were also detected. Naltrexone was still present at levels of approximately 3 ng/ml and 6-beta-naltrexol at approximately 23 ng/ml.

### DISCUSSION

#### Crude mortality

Mortality rates were found to be significantly higher in patients treated with oral naltrexone compared to those treated with implant naltrexone. While crude mortality rates in patients treated with oral naltrexone were similar to previously published rates [3,11], those for patients treated with implant naltrexone were higher than results published from two smaller studies assessing mortality outcomes associated with the same naltrexone implant preparation [23,24]. Crude mortality rates for both oral or implant treatments were comparable to other pharmacotherapies for the treatment of opiate dependence, including methadone and buprenorphine [8,10,29].

#### Gender- and age-specific mortality

Rates of mortality were found to be significantly lower in females and young patients treated with implant naltrexone compared with the oral alternatives. The low rate of mortality in young patients was treated with implant naltrexone was associated with a reduction in opiate
overdose deaths. Rates of mortality in female treated with implant naltrexone also were significantly lower than males receiving the same treatment. Such figures match with the increased rate of risky behaviour, overdose, successful suicide and greater lack of concern regarding health care associated with males, and have been reported in other drug-using populations [8,30,31].

Time following treatment
Comparison of the two treatments during the first 4 months following treatment showed that patients treated with implant naltrexone had significantly lower mortality rates (7.34 ptpy) compared to those treated with the oral naltrexone (26.28 ptpy). While patients treated with implant naltrexone would have maintained blood naltrexone levels at a therapeutic range for the first 4 months following treatment (unless the implant had been removed), the period in which oral patients remained compliant with medication is undeterminable. The length of time spent on oral naltrexone treatment is variable, with patient compliance ranging from only a few days to 6 months or more [32,33]. Hulse & Basso found that at 6 months following induction onto oral naltrexone, 51% of patients were still taking the medication daily. However, of these patients 65% had stopped using naltrexone and used heroin before returning to the naltrexone programme [33].

The notable early increased rate of mortality following induction onto oral naltrexone is similar to methadone, which has been observed to have an increased mortality rate in the 2 weeks following induction onto the treatment (up to 94.47 ptpy) [3,23,34] and following cessation (up to 48 ptpy) [8,30]. The initial increase in mortality associated with oral naltrexone is probably the result of treatment termination and return to opiate use, unlike methadone, where increased early mortality generally attributed to difficulty in determining a safe and effective starting dose (i.e. patient variation in methadone tolerance, metabolism and excretion) and the concurrent use of other central nervous system (CNS) depressant drugs such as benzodiazepines [35,36].

Cause of death
Opiate overdose was a major cause of death in the first year following treatment with oral naltrexone, while it contributed to only a small number of fatalities in patients treated with implant naltrexone. Such results concur with the previously published results indicating high rates of mortality following cessation of the oral treatment (high rates of opiate overdose death) [3,11], and support the use of a gradually tapering sustained-release naltrexone preparation in preference to the oral formulation to reduce the occurrence of fatal opiate overdoses.

Although opiate overdose death was identified in a patient treated with implant naltrexone with therapeutic naltrexone blood levels (generally accepted as 1–2 ng/ml) [37], blood morphine levels in this patient were more than 22 times the mean total morphine concentration observed in 10 fatalities involving intravenous use of morphine, with no other drugs present (mean 0.7 ng/ml, range 0.2–2.3 ng/ml) [38]. Furthermore, numerous other drugs were also present at therapeutic, subtherapeutic levels or recreational levels. In conclusion, the data suggest that while opiate overdoses can occur in patients treated with implantable naltrexone during the first 4 months following treatment, they are generally rare and require excessive levels of opiates with a probable contribution from other drugs.

Similarly, non-opiate drug mortality rates in patients treated with oral naltrexone during the first 4 months following induction were higher than in patients treated with implant naltrexone. The high level of non-opiate overdose may correspond with the high rate of combination non-opiate and opiate overdose, with the two classifications not being mutually exclusive.

The data showed no evidence to support high rates of suicide in patients treated with either oral or implant naltrexone. While suicide rates were higher than reported for the general public, they were in line with previously published rates in opiate-using populations or patients in opiate pharmacotherapies [29,39,40].

Limitations
Mortality rates obtained in this study should be considered the minimum with patients using a different name at the time of treatment, and fatalities occurring overseas possibly missed.

Additionally, differences exist between the two treatment groups. Most notably, oral treatments were carried out predominantly between 1997 and 2001. For this reason, the length of follow-up for patients treated with oral naltrexone was longer than those treated with implant naltrexone. Also, many oral patients were treated later with implant naltrexone, while very few implant patients reverted to oral naltrexone treatment.

While the data show the implant preparation to be associated with significantly less patient mortality than patients treated with oral naltrexone, this may not be true for all sustained-release naltrexone preparations. The ability of the Go Medical implant to reduce opiate overdose may be attributable to the slowly tapering pharmacokinetic profile, which
provides a long-term prophylaxis against accidental opiate overdose. In contrast, shorter-acting sustained-release naltrexone preparations whose levels peak in the days following treatment and then drop below subtherapeutic levels by 30 days may not offer the same level of protection.

CONCLUSIONS

The use of implant naltrexone appears to mitigate increases in mortality that are observed following cessation of oral naltrexone and reduce the risk of opiate overdose death during the first year following treatment. Given the reduction in mortality and previously demonstrated improved clinical efficacy of this implant naltrexone preparation compared to oral naltrexone [21], this implant has significant promise for advancing the ‘safe’ management of opiate dependence above that achieved by the use of oral naltrexone.

Declarations of interest

Study design and statistical analysis was conducted by Kelty of UWA School of Psychiatry and Clinical Neurosciences. Both authors (Kelty and Hulse) reviewed the manuscript and vouched for the completeness and accuracy of the data. Hulse has previously initiated other studies on naltrexone implants which were contracted to the University of Western Australia and funded through Federal Government Grants. Neither study author has any financial interest associated with the investigational product or Go Medical Inc. Go Medical Inc. had no right of veto or input into study design, data analysis or manuscript preparation. Funding for this study was provided by Fresh Start Recovery Programme.

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