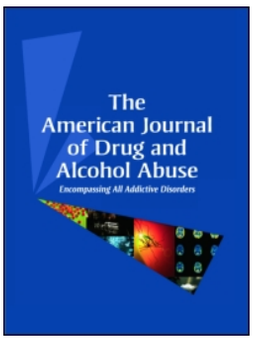

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Erin Kelty, David Joyce & Gary Hulse

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ORIGINAL ARTICLE

A retrospective cohort study of mortality rates in patients with an opioid use disorder treated with implant naltrexone, oral methadone or sublingual buprenorphine

Erin Kelty, BSc. MBioStat PhD [a,b], David Joyce, MBBS MD FRACP[c], and Gary Hulse, PhD. BBSc. (Hons)[a]

[a]Discipline of Psychiatry, University of Western Australia, Nedlands, Western Australian, Australia; [b]School of Population and Global Health, University of Western Australia, Crawley, Western Australian, Australia; [c]School of Medicine and Pharmacology, University of Western Australia, Crawley, Western Australia, Australia

ABSTRACT

Background: Sustained release naltrexone has been shown to be a safer alternative to oral naltrexone in terms of mortality in patients with an opioid use disorder; however, a direct large-scale comparison has not been made between sustained release naltrexone and the more popular opioid pharmacotherapies: methadone and buprenorphine. *Objective*: To examine and compare mortality rates in patients with an opioid use disorder treated with implant naltrexone, methadone, and buprenorphine. *Methods*: Patients treated with implant naltrexone (n = 1461, 35.6% female), methadone (n = 3515, 33.3% female), or buprenorphine (n = 3250, 34.5% female) for the first time between 2001 and 2010 in Western Australia (WA) were cross-matched against the WA Death Registry. *Results*: Crude mortality rates in patients treated with methadone (8.1 per 1000 patient years (ptpy) (HR:1.13, CI:0.82–1.55, p = 0.447) or buprenorphine (7.2 ptpy) (HR:1.01, CI:0.72–1.42, p = 0.948) were not significantly different to those treated with implant naltrexone (7.1 ptpy). Similarly, no differences were observed between the three treatments in terms of cause-specific or age-specific mortality. However, high rates of mortality were observed in methadone-treated patients during the first 28 days of treatment (HR:8.19, CI:1.08–62.21, p = 0.042) compared to naltrexone-treated patients. Female patients treated with methadone (HR:2.96, CI:1.34–6.51, p = 0.007) also experienced a higher overall mortality rate compared to naltrexone-treated patients. *Conclusions*: Crude mortality rates are comparable in patients with an opioid use disorder treated with implant naltrexone, methadone, and buprenorphine. However, implant naltrexone may be associated benefits during the first 28 days of treatment and in female patients compared to methadone.

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Introduction

Illicit opioid use is associated with high rates of mortality. Estimates of mortality rates in populations using heroin, one of most commonly used illicit opioids, range from 6.8 to 77.6 per 1000 patients years (ptpy) (1). While treating patients with an opioid use disorder generally reduces their risk of death in the long term, treatment can often be associated with short periods in which the risk is increased (2,3). These periods are usually associated with (i) changes in the use of opioid, i.e. moving from heroin to methadone (3), (ii) changes in tolerance on abstinence from opioids (4), or (iii) removal of protective influences, such as on release from prison, leaving residential rehabilitation (5,6) or ceasing treatment (3,7,8).

The use of the full μ opioid agonist, methadone, has long been the standard treatment for opioid use disorders. While methadone has been shown to improve health and social outcomes, increase treatment retention, and reduces illicit opioid use (9,10), induction onto methadone and cessation of treatment have been associated with high rates of mortality (3,11). In an Australian study, the rate of fatal accidental drug toxicity in the first 2 weeks following induction onto methadone was 70.4 ptpy, as compared with 0.72 deaths ptpy in the subsequent stable treatment period (11).

The use of buprenorphine, a partial agonist of the μ opioid receptor, is an alternative to methadone, with the qualities of efficient receptor blockade with lessened maximal receptor stimulation. That translates to a reduced potential for suppression of vital, opioid-sensitive functions such as respiration in some circumstances (12). The inclusion of naloxone in some sublingual buprenorphine formulations also serves to make the formulation unattractive as source of

CONTACT Erin Kelty erin.kelty@uwa.edu.au School of Global and Population Health, University of Western Australia, 35 Stirling Highway, Crawley WA 6009

extracted injectable opioid because the naloxone component will precipitate opioid withdrawal (13). These protective features are thought to contribute a reduction in opioid poisoning in buprenorphine-treated patients, compared to those on methadone (14,15), while still suppressing illicit drug use, reducing criminal activity, and retaining people in treatment (16). However, the protections falls short of removing the risk of lethal opioid poisoning in buprenorphine-treated patients, particularly during co-intoxication with other drugs that depress respiratory function, such as benzodiazepines and alcohol (14,17).

Naltrexone is also registered for the treatment of opioid use disorders. In contrast to methadone and buprenorphine, naltrexone is a pure opioid antagonist. The use of oral naltrexone has struggled clinically, with a lack of patient adherence with the once daily formulation reducing clinical efficacy. Additionally, patients who cease oral naltrexone treatment are reported to face an early increase in mortality, predominately from opioid poisoning (8,18). To sustain adherence with treatment, several longer acting preparations have been developed. One such preparation, a subcutaneous implant, provides therapeutic naltrexone blood levels for up to 188 days following a single treatment (19,20). The use of this implant preparation does not appear to be associated with periods of increase mortality following the treatment period, presumably due to slowly tapering release profile (18). While crude mortality rates in patients with an opioid use disorder treated with this implant have been comparable to reported rates in methadone- and buprenorphine-treated patients (18,21,22), direct comparisons of mortality have not yet been carried out (23). In this study, mortality in patients with an opioid use disorder treated with implant naltrexone was compared to patients treated with methadone or buprenorphine.

Materials and methods

Study design

This study was a retrospective longitudinal follow-up of patients with an opioid use disorder treated with implant naltrexone (n = 1461), methadone (n = 3515), and/or buprenorphine (n = 3250) using state death records to identify fatalities.

Subjects

Patients with an opioid use disorder treated with methadone or buprenorphine (Subutex® or Suboxone®) for the first time in Western Australia (WA) between January 2001 and December 2010 were identified using the WA Department of Health's Monitoring of Drugs of Dependence System (MODDS). Naltrexone implant patients were selected from records of patients with an opioid use disorder treated at a single drug and alcohol clinic in WA during the same period. This clinic was the only site in WA that routinely used sustained release naltrexone. All eligible patients were above the age of 18 and residing in WA at the time of first treatment.

Data collection

Data from the MODDS provided monthly records indicating whether a patient had received treatment within that month. Consecutive months were joined to form treatment periods. The data were then matched against the Authorization Database of the state's health department, which provided the date on which the patient was first authorized to receive treatment and the date treatment was terminated. For period without an authorization date, the commencement date was assigned the 15th of the month unless that fatality occurred before this date and then the 1st of the month was used. The last day of the final month of authorization was assigned as the termination date.

Linked data from WA Mortality Register was sourced via the WA Data Linkage System from January 2001 to December 2012 (24). This included date and cause(s) of death (ICD-10-AM codes). Additionally, toxicology data from the WA Coroner's Court was sourced for patients who had died of alcohol or other drug poisoning. Toxicology reports provided the identities of drugs detected in blood specimens collected at the time of mortuary admission or at the time of post-mortem examination, as revealed by specific chromatographic – mass spectrometric assays, for each death.

Data analysis

Crude mortality rates in patients treated with implant naltrexone were compared with patients treated with methadone or buprenorphine using Cox proportional hazard regression. Some patients had passed through more than one treatment modality during the study period, so treatment was treated as a time varying covariate. However, patients who appeared to be on more than one treatment at a time, presumably arising from imprecision in dating authorizations around the time of changing therapies, were excluded from analysis. A multivariate analysis was also performed controlling for age at first treatment, gender, and year of first

treatment. Additionally, gender-specific, age-specific (age at the commencement), and cause-specific mortality rates were calculated and compared using Cox proportional hazard regression.

Cause-specific mortality rates were based on the International Classification of Diseases, 10th Revision (ICD-10) codes assigned to each fatality. Both primary and secondary causes were utilized, with up to nine ICD-10 codes available for each death. The forensic pathologist's description of the cause of death was adopted where ICD-10 codes were unavailable. These causes included drug poisoning (T36 - 51), suicide (X60 – X84, Y87.0), respiratory disease (J00 – J99), cardiovascular disease (I00 – I99), traffic/transport related (V00 – V99), and cancer (C00 – C99). Additional drug-specific mortality rates were calculated using the results of individual post-mortem toxicology.

The influence of treatment phase on mortality was also examined, allocating deaths into the induction period, on-treatment period, and off-treatment period. The induction period included the first 28 days of treatment, as this is considered a time of high risk, particularly for patients on methadone. The commencement of treatment for naltrexone patients was the day the implant was inserted, although patients may have received treatment in the days and weeks before to prepare them for naltrexone treatment. The on-treatment period commenced at day 29 and, for methadone and buprenorphine, ceased at the termination date. For naltrexone, the on-treatment period was deemed to end at 182 days post implantation, based on the pharmacokinetic profile of the implant and efficacy data (19,25,26). However, due to patient variation in pharmacokinetics of implant naltrexone, a patient who transitioned onto methadone or buprenorphine between 121 and 181 days was allocated that day for the start of the new treatment. This reflects the assumption that naltrexone levels had already become ineffective. The off-treatment period commenced at the cessation of a treatment, and continued until the patient received a new treatment, died, or up to 31st December 2012.

Ethics

This study protocol was reviewed and approved by the Department of Health Human Research Ethics Committee (2012/63) and the University of Western Australia Human Research Ethics Committee (RA/4/1/1864).

Results

Demographics

The three groups had greater number of males than females, with first treatment generally commencing in their late 20's and early 30's (Table 1). Of the patients treated with an opioid pharmacotherapy, 29.7% of patients had been on two pharmacotherapies, while 8.3% had been on all three pharmacotherapies.

All-cause mortality

A total of 317 deaths were observed during follow-up. Crude mortality rates in patients treated with methadone (HR:1.13, CI:0.82–1.55, $p = 0.447$) or buprenorphine (HR:1.01, CI:0.72–1.42, $p = 0.948$) were not significantly different to patients treated with implant naltrexone. Similarly, when adjusted for age, gender, and year of first treatment, there was no significant difference between mortality in patients treated with methadone (HR:1.08, 95%CI:0.78–1.48, $p = 0.642$) or buprenorphine (HR:0.97, 95%CI:0.69–1.36, $p = 0.851$) compared to implant naltrexone.

Treatment period specific mortality

There was also no significant difference in the mortality rates of buprenorphine- and naltrexone-treated patients over the overall time that included the induction period on-treatment time and off-treatment time. However, specifically during the induction period, rates of mortality in methadone-treated patients were significantly higher than naltrexone-treated patients (HR:8.19, CI:1.08–62.21, $p = 0.042$). During on-treatment and off-treatment periods, there was no significant difference between methadone and naltrexone mortality rates.

Age- and gender-specific mortality

While mortality rates increased with increasing age, there was no significant difference between mortality

Table 1. Demographics of opiate dependent patients treated with implant naltrexone, methadone, and buprenorphine.

	Naltrexone	Methadone	Buprenorphine
Number	1461	3515	3250
% Male	64.4	66.7	65.5
Age ± st dev.	30.3 ± 7.9	31.9 ± 8.4	31.5 ± 8.3
Period of exposure (yrs)[1]	1.0 ± 0.8	2.5 ± 2.6	1.9 ± 2.4
Period of follow up (yrs)[2]	4.9 ± 3.3	5.5 ± 3.3	4.5 ± 3.4

1. Period of exposure to the opioid pharmacotherapy (on treatment and the transition period)
2. From commencement of treatment to the start of a new treatment, death or 31st December 2012

rates in naltrexone, methadone, or buprenorphine treatment groups within any of the age groups.

For males, the mortality rate in patients treated with methadone (HR:0.83, CI:0.58–1.18, $p = 0.300$) and buprenorphine (HR:0.83, CI:0.57–1.20, $p = 0.323$) compare to patients treated with implant naltrexone. However, female patients treated with methadone had a significantly higher mortality rate compared with women treated with implant naltrexone (HR:2.96, CI:1.34–6.51, $p = 0.007$), but there was no significant difference between women treated with buprenorphine and implant naltrexone (HR:2.03, CI:0.88–4.64, $p = 0.095$). The difference in mortality rates in females treated with methadone and naltrexone did not seem to arise from difference in mortality from drug poisoning or suicide. The causes of death, as revealed by ICD-10 codes, did not differ significantly between the naltrexone-, methadone-, or buprenorphine-treated groups. (Table 2).

Cause-specific mortality

Of the 317 fatalities, 147 (47.0%) involved alcohol or another drug. The involvement of specific drug groups in death was examined, using the results of post-mortem blood toxicological analyses. As expected, patients in the methadone and buprenorphine treatment groups were more likely to have their treatment drug present in post-mortem blood, if they died during an on-treatment period. Also as expected, opioid and benzodiazepine drugs were most prominently represented in all three treatment groups. Some differences in the relative incidences of particular drugs were apparent, though. The presence of total morphine (HR:0.52, CI:0.31–0.88, $p = 0.014$) and evidence for recent heroin use (HR:0.50, CI:0.26–0.97, $p = 0.041$) were less common in methadone-treated patients, compared to naltrexone-treated patients, but these differences mostly arose from exposure that occurred after the cessation of treatment (Table 3). The groups were similarly exposed to benzodiazepines generally and diazepam specifically, but the potent benzodiazepine, alprazolam, was less commonly present in buprenorphine naltrexone-treated patients, compared to naltrexone-treated patients (HR:0.30, CI:0.10–0.92, $p = 0.035$). All deaths in naltrexone-treated patients that involved alprazolam occurred following the cessation of treatment. The semisynthetic opioid, oxycodone, was found significantly more often in buprenorphine-treated patients dying on treatment than in naltrexone-treated patients dying on treatment, but numbers were low. Alcohol was also found more often in deaths in patients treated with methadone, compared to those treated with naltrexone (HR:4.37, CI:1.00–19.00, $p = 0.049$), largely due to differences occurring during off-treatment periods.

The effectiveness of any treatment was evident in comparisons of overall drug-related mortality in patients who were on treatment, compared with those who had ceased treatment (HR:1.47, CI:1.16–1.88, $p = 0.002$). These reduced rates arose from significantly reduced rates for opioid drugs generally, and specifically for morphine (free and total) and heroin in the on-treatment subgroups. There was a higher rate of methadone presence in on-treatment patient deaths, but this was largely due to the methadone-treated patients in the overall on-treatment group. There was an accompanying increased incidence of benzodiazepine drugs among patients dying off-treatment, compared with those dying on treatment, largely accounted for by an increased prevalence of diazepam.

After alcohol and other drug-related cause of death, suicide was the second most common diagnosis, accounting for 14.5% of deaths ($n = 46$) (Table 2). Of those with a suicide diagnosis, 30.4% ($n = 14$) also had an alcohol or other drug diagnosis. There was no significant difference between the three treatments in terms of fatalities as a result of suicide. Similarly, there was no significant difference in rates of cardiovascular or respiratory deaths between the three treatments. Of the death with a cardiovascular or respiratory diagnosis, 29.4 and 41.0% also had an alcohol or other

Table 2. Mortality rates (95% confidence intervals) in opiate dependent patients treated with implant naltrexone, compared with patients treated with methadone or buprenorphine (per 1000 patient years).

	Naltrexone	Methadone	Buprenorphine
Crude mortality	7.1 (5.3–9.4)	8.1 (6.9–9.5)	7.2 (5.9–8.7)
0–1 year	1.1 (0.1–7.6)	5.6 (2.5–8.6)	4.6 (2.5–8.6)
0–5 years	6.2 (4.3–9.1)	7.6 (6.2–9.3)	6.9 (5.4–8.8)
0–10 years	7.4 (5.6–9.7)	8.0 (6.8–9.4)	7.2 (6.0–8.8)
Mortality during treatment periods			
Induction	4.3 (0.1–24.1)	32.3 (18.5–52.5)*	4.1 (0.5–14.9)
On treatment	6.5 (2.8–12.9)	5.1 (3.7–6.9)	4.6 (3.0–6.7)
Off treatment	7.4 (5.3–10.0)	9.4 (7.6–11.4)	9.1 (7.2–11.3)
Gender			
Female	2.7 (1.1–5.6)	8.1 (6.1–10.6)**	5.6 (3.7–8.1)
Male	9.7 (7.0–13.0)	8.1 (6.6–9.8)	8.0 (6.3–10.0)
Age of treatment			
18–25	3.6 (1.3–7.8)	6.1 (3.9–9.0)	5.2 (3.0–8.4)
26–35	7.9 (5.2–11.4)	7.5 (5.8–9.5)	5.9 (4.2–8.0)
36–45	8.2 (4.1–14.7)	9.2 (6.6–12.5)	9.6 (6.7–13.4)
46+	10.8 (4.0–23.5)	13.2 (8.5–19.7)	12.6 (7.0–20.8)
Cause			
Drug and alcohol	4.0 (2.7–5.8)	3.4 (2.6–4.3)	3.7 (2.8–4.8)
Suicide	1.3 (0.6–2.4)	1.2 (0.7–1.8)	0.9 (0.5–1.5)
Respiratory	1.3 (0.6–2.4)	1.0 (0.6–1.5)	0.7 (0.4–1.3)
Cardiovascular	0.6 (0.2–1.5)	0.9 (0.5–1.4)	0.8 (0.4–1.4)
Traffic	0.6 (0.2–1.5)	0.3 (0.1–0.7)	0.3 (0.1–0.7)
Cancer	0.4 (0.1–1.3)	0.4 (0.1–0.7)	0.4 (0.1–0.9
Undetermined	0.9 (0.3–1.9)	1.6 (1.1–2.3)	0.6 (0.3–1.2)

*$p < 0.05$,**$p < 0.001$ *compared with naltrexone-treated patients, no adjustments made for multiple comparisons*

Table 3. Rates of drug specific mortality on treatment (including the induction) and off-treatment for methadone, buprenorphine and naltrexone (per 1000 patient years).

	Naltrexone			Methadone			Buprenorphine			Combined[1]		
	All	Ind/On	Off	All	Ind/On	Off	All	Ind/On	Off	All	Ind/On	Off
Any	4.0	2.1	4.5	3.4	2.9	3.7	3.7	1.5	5.2	3.6	2.3	4.4**
Opioid	3.9	1.4	4.5	2.9	2.6	3.2	3.3	1.1	4.8	3.2	1.9	4.0**
- Morphine (total)[1]	3.4	1.4	4.0	1.8*	0.9	2.6	2.2	0.2	3.7	2.2	0.7	3.3***
- Morphine (free)	2.7	1.4	3.1	1.6	0.8	2.4	2.2	0.2	3.6	2.0	0.6	3.0***
- Heroin[2]	2.1	0.7	2.5	1.1*	0.7	1.4	1.6	0.2	2.6	1.4	0.5	2.1***
- Methadone	0.9	0.0	1.1	1.3	2.5***	0.3	0.4	0.2	0.6	0.9	1.4	0.6**
- Oxycodone	0.6	0.0	0.7	0.4	0.2	0.6	0.4	0.3***	0.5	0.4	0.2	0.6
- Buprenorphine	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.3***	0.0	0.0	0.1	0.0
- Fentanyl	0.1	0.0	0.2	0.1	0.0	0.2	0.1	0.0	0.1	0.1	0.0	0.2
Alcohol	0.4	0.7	0.4	1.2	0.8	1.5*	0.8	0.3	1.2	0.9	0.6	1.1
Benzodiazepine	2.7	1.4	3.1	2.6	2.5	2.6	2.9	1.1	4.2	2.7	1.9	3.3*
- Diazepam/met.	2.4	1.4	2.7	2.4	2.5	2.3	2.8	1.1	3.9	2.7	1.9	3.0*
- Alprazolam	1.1	0.0	1.4	0.5	0.3***	0.6	0.3*	0.2	0.5	0.5	0.2	0.7
THC/met.	0.9	1.4	0.7	1.0	0.6	1.4	0.9	0.3	1.3	0.9	0.5	1.2
Methamph.	1.0	0.7	1.1	0.5	0.2	0.7	0.9	0.5	1.2	0.9	0.4	0.9
Amphetamines	0.9	0.7	0.9	0.5	0.3	0.7	0.9	0.5	1.2	0.7	0.4	0.9

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ compared with naltrexone-treated patients), not adjusted for multiple comparisons
1. Comparison between on and off treatment mortality rates.
2. Cases where heroin is judged to have been the source of the last ante-mortem administration of natural opioid.

drug diagnosis, respectively. There was also no significant difference between the treatments in cancer (n = 16, 5.1%) or traffic accidents (n = 14, 4.4%) specific mortality rates. Deaths with an undeterminable diagnosis made up 14.5% of deaths (n = 46).

Discussion

This study gives insight into mortality outcomes in parallel groups of patients with an opioid use disorder treated with methadone, buprenorphine or implant naltrexone, during treatment and after withdrawal from treatment. The crude mortality rates in the groups were comparable, supporting a judgment that implant naltrexone is a safe alternative to either of the opioid agonist therapies. There was a consistent finding across the three groups that mortality was lower at times when patients were engaged with treatment than when they had withdrawn from treatment. The degree of apparent protection was similar for the three treatments. Not surprisingly, the increased overall mortality off treatment found a ready explanation in the prevalence of opioid drugs in post-mortem toxicology.

The comparison between induction, treatment, and off-treatment phases also gave a measure of the increased risk that accompanies the induction phase for methadone. There was an approximately three-fold increase in mortality during the first 28 days of methadone treatment. Earlier studies have shown even more dramatically enhanced risk (11). The increased mortality is linked to an increased rate of opioid poisoning, which may be reduced by patient education and making naloxone available to patients and their associates for emergency use (11,22,27). This induction phase effect was not seen in the buprenorphine and implant naltrexone groups in this study.

Similar mortality benefits for the three treatments were found in each of the age group categories. There was, however, a significantly increased mortality among methadone-treated women compared with naltrexone-treated women of approximately three-fold. It was not linked to increased mortality from the most common causes of death, that is, drug toxicity and suicide. The increased mortality in women of the methadone-treated group (8.1 ptpy) gave that group a similar mortality to males (8.0 ptpy), which contrasts with the more generally observed higher male mortality in substance users. However, comparable rates of mortality have been observed in male and female patients treated with methadone (22,28,29), particularly during active treatment (28). Higher male mortalities were observed in both the buprenorphine and implant naltrexone groups. The higher male mortality is linked to an increased incidence of drug toxicity death, estimated at 1.7 times the female rate in one study (1). Privacy constraints on our study prevented further exploration of this observation, to determine whether this greater female mortality reflected non-random diversion of particularly vulnerable women into methadone treatment.

Drug toxicity and suicide were prominent among the causes of death in all groups. They did not differ in overall incidence between the three groups, though members of the methadone and buprenorphine treatment groups were more likely to have those treatment drugs detected in post-mortem toxicology, as expected. Opioids

and benzodiazepines were the most common non-treatment drugs detected in post-mortem toxicology, consistent with prior experience. The drug class exposure profiles were also generally similar between the three treatment groups, implying that no treatment had superior protective effect with any particular drug intoxicant. There were some differences in the detection incidences of specific opioids and benzodiazepines between the treatment groups, but not systematically throughout all phases. Evidence for morphine or heroin use was more common among deaths in the naltrexone group compared to the methadone group, but largely as a result of use after withdrawal from treatment. The difference did not extend to the buprenorphine group. The potent benzodiazepine, alprazolam, was more common among deaths in the methadone group and the synthetic opioid, oxycodone, was more common in the buprenorphine group. The numbers were small in each case. Alcohol was less commonly present in the post-mortem toxicology of patients in the naltrexone-treated group. Naltrexone is effective in assisting alcohol abstinence dependence (30), but most of the deaths in the naltrexone group occurred after withdrawal from treatment, when an ongoing benefit would not be expected.

The three treatments were comparable in terms of mortality relating to non-alcohol and other drug-related poisoning. However, there may be differences when examined more closely in terms of treatment periods, gender, and age.

Limitations of the study

This study utilized a state health mortality dataset and thus fatalities that occurred outside of WA may not have been included. Additionally, we did not have data on deaths occurring while preparing for induction onto implant naltrexone treatment, which has been identified as a potentially high risk period. Rates of cause-specific mortality should also be taken as a minimum because deaths that were classified as of undetermined cause, and not allocated a coded cause of death, were excluded from consideration (14.5% of deaths).

Factors such as age and sex were controlled in the analysis, but allocation to the groups was by choice, not by randomization. Differences may therefore have existed, related perhaps to motivation, preparedness to risk a novel therapy (implantable naltrexone) or a history of failure in opioid agonist programs.

Conclusions

Implant naltrexone may provide a suitable alternative to methadone and buprenorphine for the treatment of opioid use disorders, with implant naltrexone not associated with an increased risk of mortality. The use of implant naltrexone may be preferential to methadone for the treatment of female patients, given the lower incidence of mortality in female patients treated with implant naltrexone. Given the limitations of this study in terms of the use of retrospective data (e.g. selection bias) more tightly controlled prospective comparisons are required.

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ORCID

Erin Kelty http://orcid.org/0000-0002-0841-2216

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