International Journal of Drug Policy 46 (2017) 54–60

Contents lists available at ScienceDirect

International Journal of Drug Policy

journal homepage: www.elsevier.com/locate/drugpo

Research paper

Fatal and non-fatal opioid overdose in opioid dependent patients treated with methadone, buprenorphine or implant naltrexone

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ARTICLE INFO

Article history:
Received 18 August 2016
Received in revised form 16 December 2016
Accepted 12 May 2017
Available online xxx

Keywords:
Methadone
Buprenorphine
Naltrexone
Overdose

ABSTRACT

Background: Illicit opioid use is associated with high rates of fatal and non-fatal opioid overdose. This study aims to compare rates of fatal and serious but non-fatal opioid overdose in opioid dependent patients treated with methadone, buprenorphine or implant naltrexone, and to identify risk factors for fatal opioid overdose.
Methods: Opioid dependent patients treated with methadone (n = 3515), buprenorphine (n = 3250) or implant naltrexone (n = 1461) in Western Australia for the first time between 2001 and 2010, were matched against state mortality and hospital data. Rates of fatal and non-fatal serious opioid overdoses were calculated and compared for the three treatments. Risk factors associated with fatal opioid overdose were examined using multivariate cox proportional hazard models.
Results: No significant difference was observed between the three groups in terms of crude rates of fatal or non-fatal opioid overdoses. During the first 28 days of treatment, rates of non-fatal opioid overdose were high in all three groups, as were fatal opioid overdoses in patients treated with methadone. However, no fatal opioid overdoses were observed in buprenorphine or naltrexone patients during this period. Following the first 28 days, buprenorphine was shown to be protective, particularly in terms of non-fatal opioid overdoses. After the cessation of treatment, rates of fatal and non-fatal opioid overdoses were similar between the groups, with the exception of lower rates of non-fatal opioid overdose in the naltrexone treated patients compared with the methadone treated patients. After the commencement of treatment, gender, and hospitalisations with a diagnosis of opioid poisoning, cardiovascular or mental health problems were significant predictors of subsequent fatal opioid overdose.
Conclusions: Rates of fatal and non-fatal opioid overdose were not significantly different in patients treated with methadone, buprenorphine or implant naltrexone. Gender and prior cause-specific hospitalisations can be used to identify patients at a high risk of fatal opioid overdose.

Introduction

Opioid overdoses are typically the result of opioid induced respiratory depression, resulting in hypoxia, and in some instances death. It is generally presumed that opioid poisoning occurs as a result of the excessive consumption of opioids. However, while this may be the case in a small proportion of deaths, toxicological analysis has repeatedly found that blood morphine levels in fatal opioid poisoning are similar to individuals who have recently used opioids but died of alternative causes (Darke, Duflou, & Kaye, 2007; Darke, Ross, Zador, & Sunjic, 2000; Meissner, Recker, Reiter, Friedrich, & Oehmichen, 2002). Similarly, while intentional self-harm is not uncommon in opioid dependent patients, self-administration of a high dose of opioids as a method of attempted suicide is relatively rare. A study by Heale, Dietze, and Fry (2003), interviewed 256 heroin overdose survivors who were successfully revived by paramedics finding that only 9 (3.5%) had intentionally attempted to overdose (Heale et al., 2003).

The occurrence of opioid poisoning has been associated with changes in tolerance. Tolerance to opioids develops quickly, with evidence of tolerance to morphine exhibited as early as 8 h during continuous intravenous infusions in rats (Kissin, Brown, Robinson, & Bradley, 1991; Ling, Paul, Simantov, & Pasternak, 1989). Following periods of abstinence, the tolerance built over periods of regular use is reversed and the opioid system up-regulates and re-sensitizes to an approximate pre-opioid use level. Such changes can occur within several days, with an abstinence period of

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http://dx.doi.org/10.1016/j.drugpo.2017.05.039
0955-3959/

5.4 days required to regenerate 50% of the intrinsic responsivity lost during the development of tolerance in fully tolerant morphine rats (Ouellet & Pollack, 1995). Upon return to use, opioid users may fail to reduce their opioid dose to accommodate reduced tolerance, resulting in overdose. Such changes account for significant increases in opioid poisoning mortality following release from prison and in-patient rehabilitation (Merrall et al., 2010; Ravndal & Amundsen, 2010; Strang et al., 2003). In addition, it appears that an individual's tolerance to the respiratory depressant effects of opioids does not necessarily develop at the same rate as tolerance to its euphoric and analgesic effects, making it harder for returning opioid users to calculate a safe dose (White & Irvine, 1999).

While opioids alone can cause sufficient respiratory depression to cause hypoxia, the co-ingestion of other CNS depressant drugs such as alcohol and benzodiazepines has been found to play a significant role in a large percentage of opioid overdoses (Gutiérrez-Cebollada, de la Torre, Ortuño, Garcés, & Camí, 1994; Zador, Sunjic, & Darke, 1996). In an examination of 953 heroin-related fatalities, 46% of cases had alcohol present, while benzodiazepines was present in 27% (Darke et al., 2000).

The pharmacotherapies used to treat opioid dependence have also been linked to opioid poisoning. The long acting opioid agonist, methadone, has been associated with high rates of opioid poisoning in the first two to four weeks following induction onto treatment, and in the first two weeks following cessation of treatment, as changes in dose and tolerance occur (Buster, Brussel, & Brink, 2002; Davoli et al., 2007; Degenhardt et al., 2009; Kimber, Larney, Hickman, Randall, & Degenhardt, 2015). Similarly, the opioid antagonist naltrexone has been associated with high rates of opioid poisoning mortality, following the cessation of treatment, due to a reduction of opioid tolerance and a rapid unblocking of mu opioid receptors following cessation of oral dosing (Kelty & Hulse, 2012).

A number of pre-existing health conditions are also likely to be factors associated with the occurrence of opioid poisoning, including hepatic and respiratory disease/disorders. It is hypothesised that hepatic diseases would result in reduced hepatic clearance of opioids in patients with liver damage, resulting in prolonged exposure to increased levels of opioids (Warner-Smith, Darke, Lynskey, & Hall, 2001), while respiratory disease/disorders may increase the risk of overdoses given the role of the respiratory system (Overland, Nolan, & Hopewell, 1980).

The aim of this study is to examine the characteristics of both fatal and non-fatal opioid poisoning in opioid dependent patients, following entry into an opioid pharmacotherapy. Additionally, the study aims to examine the risk factors associated with fatal opioid poisoning, including previous opioid and non-opioid poisoning, intentional self-harm, and cardiovascular and respiratory hospital admissions.

Methods

Design

The study was a retrospective-prospective cohort study, examining opioid dependent patients routinely treated with methadone, buprenorphine or implant naltrexone using state health hospital and mortality data sets.

Patients

The study comprised of 5646 opioid dependent patients, 3515 treated with methadone, 3250 treated with buprenorphine and 1461 treated with implant naltrexone. These patients had been treated for the first time in Western Australia (WA) between 2001 and 2010 inclusive. Patients were required to be at least 18 years of age at the time of first treatment and residing in WA. Patients treated with methadone and buprenorphine were obtained from the Monitoring of Drugs of Dependence System, managed by the WA Department of Health. Patients treated with implant naltrexone were obtained from patient treatment lists from a drug and alcohol clinic.

Data linkage

Identifying patient information was provided to the WA Data Linkage Branch, where it was linked with state hospital, emergency and mortality datasets. The data was then de-identified and provided to the research team.

Data analysis

ICD-10-AM codes assigned to hospital and mortality records were used to identify events that occurred as a result of an opioid poisoning (T40.0–T40.4). Rates of fatal and non-fatal (requiring hospital admission) opioid poisoning were calculated for each group and expressed per 1000 patient years (ptpy). Comparisons of rates of fatal opioid poisoning between the three groups was carried out using univariate Cox Proportional Hazard Regression, while rates of non-fatal opioid poisoning were compared using Generalised Estimating Equations, with a negative binomial distribution and a log link. Pre and post-treatment incidence rates of hospital admissions with a diagnosis of opioid poisoning were compared using Generalised Estimating Equations.

Rates of fatal and non-fatal opioid overdoses and the ratio of the two were also calculated for patients during the 'induction', 'on treatment' and 'off treatment' periods. The 'induction' period was defined as the first 28 days after commencing treatment, while the 'on treatment' period followed on from the induction period to the cessation of treatment. Only treatment periods in which the average dose were $\geq$20 mg for methadone and $\geq$2 mg for buprenorphine were included. For patients treated with implant naltrexone, the treatment was deemed to have ceased at 182 days following the initial treatment, in line with pharmacokinetic and efficacy studies (Hulse, Morris, Arnold-Reed, & Tait, 2009; Ngo, Arnold-Reed, Hansson, Tait, & Hulse, 2008). However, due to patient variation in metabolism of naltrexone, if a patient transitioned onto methadone or buprenorphine between 121 and 181 days, this was used as the treatment period, as it was assumed that to transition onto either treatment, naltrexone levels would need to be negligible. In two fatalities, methadone was present at therapeutic doses within a week of the patients having ceased methadone. However the treatment data suggested they only received one day of treatment. It was deemed most likely that these patients were still on treatment at the time of death. For all three treatments, 'off' treatment was calculated from the cessation of the 'on' treatment period to the commencement of a subsequent treatment or 31/Dec/2012.

Characteristics of fatal and non-fatal opioid overdose were ascertained from mortality and hospital records and collated for each treatment (overall, on and off treatment) and expressed ptpy. Characteristics examined included gender, diagnosis of non-opioid drug poisoning (T36–39.9, T40.5–51), intentional self-harm (X60–X84, Y87.0), respiratory disease (J00–J99) or cardiovascular disease (I00–I99). Simple logistic regression was used to compare the prevalence of these characteristics in each treatment group.

Univariate and multivariate Cox proportional hazard regression was used to identify potential risk factors for fatal opioid overdose. Risk factors examined included gender, age at first treatment, hospital admissions for opioid overdose, non-opioid drug

overdose, intentional self-harm, cardiovascular or respiratory problems in the two years prior to initial treatment and following the commencement of initial treatment (time varying covariate).

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).

Findings

Cohort characteristics

Patients treated with the methadone, buprenorphine and naltrexone were predominantly male and aged in their early 30's at the commencement of treatment (Table 1). In the 12 months prior to admission to any opioid pharmacotherapy, rates of non-fatal opioid overdoses were not significantly different between the three groups.

Overall 117 deaths and 658 hospital admissions were assigned a diagnosis of opioid poisoning. Of the hospital admissions, the death of the patient occurred in 14 admissions (2.1%). Comparisons of pre- and post-treatment rates of opioid poisoning requiring hospital admission (including fatal admissions) showed a statistically significant reduction in patients treated with buprenorphine (RR 0.66, CI: 0.51–0.84). No significant reductions in rates of hospitalisation were observed in methadone (RR: 1.08, CI: 0.85–1.37) or naltrexone patients (RR: 0.75, CI: 0.50–1.12).

Overdose characteristics of fatal and non-fatal opioid poisoning

Overall 117 fatalities involving opioid poisoning were observed, equating to 2.8 deaths per 1000 patient years (ptpy), with no significant difference in the rate of fatal opioid poisoning in patients treated with methadone, buprenorphine or implant naltrexone (Table 2). The most common co-diagnoses included a poisoning with a non-opioid drug (69.2%), respiratory diagnosis (12.0%), intentional self-harm (8.5%) and cardiovascular diagnosis (6.0%). The presence of co-diagnoses did not differ significantly between the three opioid pharmacotherapies overall, with the exception of lower rates of non-opioid drug poisoning in fatalities in patients treated with buprenorphine compared with methadone ($p = 0.040$). Fatalities occurring in hospital (including emergency department) made up only a small proportion of fatalities, with only 8.2% of methadone, 14.3% of buprenorphine and 7.7% of naltrexone patients.

In comparison, 644 non-fatal opioid poisonings were observed, equating to 15.6 ptpy and 5.70 non-fatal opioid poisonings for every fatal poisoning. Of opioid overdose admission, 10.4% required admission to ICU staying an average of 2.2 days (range: 1–18 days). The average hospital length of stay was 3.8 days (range: 1–137 days). As per fatal opioid overdoses, there was no significant difference in the rate of non-fatal opioid poisoning in the three treatment groups. The most common co-diagnoses were non-opioid drug poisoning (55.4%), intentional self-harm (48.0%), respiratory disorder (7.8%) and cardiovascular disorder (6.1%). The presence of co-diagnoses did not differ significantly between methadone and naltrexone, however buprenorphine had fewer overdoses involving non-opioid drug poisoning ($p = 0.048$) and intentional self-harm (0.045).

Gender

No significant reduction in non-fatal opioid overdoses were observed in male patients treated with methadone (RR: 1.07, CI: 0.73–1.57), buprenorphine (RR: 0.77, CI: 0.55–1.09) or naltrexone (RR: 1.25, CI: 0.62–2.51). However in female patients, there was a significant reduction in patients treated with buprenorphine (RR: 0.49, CI: 0.34–0.71) and naltrexone (RR: 0.52, CI: 0.32–0.87), but not methadone (RR: 0.93, CI: 0.67–1.30).

Rates of fatal opioid overdose were significantly elevated in male patients treated with naltrexone compared to those treated with methadone (HR: 1.80, CI: 1.06–3.06), however rates of opioid overdose in male patients treated with buprenorphine were not significantly different to methadone (HR: 1.24, CI: 0.77–1.99). In female patients, rates of fatal opioid overdose in methadone treated patients were not significantly different to either buprenorphine (HR: 0.92, CI: 0.39–2.16) or naltrexone (HR: 0.80, CI: 0.26–2.44). No significant difference was observed in terms of non-fatal opioid overdoses in either males or females (Table 3).

Treatment periods

During the induction period (first 28 days after commencing treatment), rates of hospital admissions for non-fatal opioid poisoning were consistent across the three treatments and were approximately double that of patients while 'on treatment' (after the first 28 days of treatment). While no opioid fatalities were observed in the induction period in patients treated with buprenorphine or implant naltrexone, high rates of fatal opioid poisoning were observed in patients treated with methadone (16.2 ptpy). In the methadone cohort, for every 1.75 hospitalisations for opioid poisoning 1 patient died of the same cause. Both fatal and non-fatal opiate overdoses occurred predominantly in the first two weeks following the commencement of treatment, with a median time to fatal opioid overdose of 5.5 days (interquartile range: 4.25–8.50) and 6.5 days (interquartile range: 3.5–9.25) for non-fatal opioid overdoses.

Although the naltrexone cohort was comprised of 64.4% males, males only made up 16.7% of the patients who were admitted to hospital with a non-fatal opioid poisoning. In contrast, males made up 78.6% and 64.3% of patients admitted to hospital in the methadone and buprenorphine cohorts respectively.

Table 1
Opioid dependent patients treated with methadone, buprenorphine or implant naltrexone for the first time between January 2001 and December 2010 in Western Australia.

	Methadone	Buprenorphine	Naltrexone
Number	3515	3250	1461
Male (%)	66.7	65.5	64.4
Start age ± st dev.	31.9 ± 8.4	31.5 ± 8.3	30.3 ± 7.9
Average period of exposure (yrs) ± st dev.	1.0 ± 0.8	2.5 ± 2.6	1.9 ± 2.4
Average follow-up ± st dev.	5.5 ± 3.3	4.5 ± 3.4	4.9 ± 3.3
Median dose per treatment (mg) (IQR)	NA	47.0 (34.6–65.0)	13.0 (8.0–20.0)
Median treatment length per episode (yrs) (IQR)	0.50 (0.46–0.50)	0.63 (0.18–1.72)	0.30 (0.10– 0.99)
Pre-treatment opioid poisoning (ptpy)[a]	18.5	24.0	20.5

St dev. = standard deviation, yrs = years, ptpy = per 1000 patient years, IQR = interquartile range.
[a] Rate of hospital admissions for opioid poisoning in the 12 months prior to commencing any opioid pharmacotherapy.

Table 2
Co-diagnoses associated with fatal and serious but non-fatal opioid overdoses in opioid dependent patients treated with methadone, compared with those treated with buprenorphine or implant naltrexone.

	Methadone			Buprenorphine			Naltrexone		
	Fatal	Non-fatal	Ratio	Fatal	Non-fatal	Ratio	Fatal	Non-fatal	Ratio
Total									
Rate	2.5	16.8	6.67	2.9	14.5	5.10	3.7	14.7	3.96
% Non-opioid drugs	79.6	59.0	0.74	59.5*	53.3*	0.89	65.4	48.5	0.74
% Intentional self-harm	10.9	52.3	4.81	7.3	43.5*	5.94	7.7	43.7	5.68
% Cardiovascular	6.5	6.1	0.94	5.6	7.3	1.15	7.7	6.8	0.88
% Respiratory	17.4	7.3	0.42	7.3	8.4	1.15	11.5	7.8	0.67
Induction (0–28 days)									
Rate	16.2	28.3	1.75	0.0	28.9	–	0.0	26.0	–
% Non-opioid drugs	50.0	42.9	0.86	0.0	64.3	–	0.0	83.3	–
% Intentional self-harm	12.5	28.6	2.29	0.0	57.1	–	0.0	66.7	–
% Cardiovascular	12.5	7.1	0.57	0.0	0.0	–	0.0	0.0	–
% Respiratory	12.5	7.1	0.57	0.0	0.0	–	0.0	16.7	–
On-treatment (+29 days)									
Rate	1.5	10.5	6.77	0.7	6.6*	9.25	1.6	10.6	6.50
% Non-opioid drugs	76.9	58.0	0.75	50.0	51.4	1.03	50.0	53.8	1.08
% Intentional self-harm	7.7	46.6	6.06	0.0	43.2	–	50.0	46.2	0.92
% Cardiovascular	7.7	4.5	0.59	0.0	2.7	–	0.0	7.7	–
% Respiratory	38.5	10.2	0.27	0.0	0.0	–	0.0	15.4	–
Off-treatment									
Rate	2.6	21.3	7.76	4.3	18.9	4.49	4.3	15.1**	3.50
% Non-opioid drugs	89.3	60.4	0.68	60.5*	52.8	0.87	62.5	45.2*	0.68
% Intentional self-harm	10.7	56.0	5.23	7.9	42.3**	5.36	4.2	41.7*	10.00
% Cardiovascular	3.6	6.7	1.87	5.3	6.7	1.28	8.3	7.1	0.86
% Respiratory	7.1	6.2	0.87	7.9	11.0	1.40	12.5	6.0	0.48

* $p < 0.05$.
** $p < 0.001$.

While on treatment, buprenorphine was shown to be protective against opioid poisoning with 9.25 non-fatal opioid poisoning admissions for every fatal opioid poisoning, compared with 6.77 for methadone and 6.50 for naltrexone. Buprenorphine also had significantly fewer admissions for non-fatal opioid poisoning ($p = 0.018$) compared with methadone.

In patients on treatment, intentional self-harm appeared to play a significant role in the occurrence of non-fatal poisoning overdoses but was rare as a co-diagnosis of fatal opioid overdose. Respiratory disease/disorder was a common co-diagnosis in fatalities involving opioid poisoning in patients on methadone treatment (38.5%), however this was absent in fatalities in patients on buprenorphine or naltrexone.

Rates of fatal opioid poisoning were not significantly different between the three groups, however rates of non-fatal opioid poisoning were significantly lower in naltrexone treated patients than in methadone treated patients following treatment ($p < 0.001$). Following treatment, non-fatal opioid overdoses in naltrexone treated patients were comprised of fewer overdoses involving non-opioid drugs ($p = 0.017$) and intentional self-harm ($p = 0.026$) compared with methadone treated patients. Non-fatal opioid overdoses in buprenorphine patients had fewer non-fatal overdoses with a co-diagnosis of intentional self-harm ($p = 0.008$) and fewer fatal overdoses involving non-opioid drugs ($p = 0.026$) compared with methadone.

Table 3
Gender difference in rates of fatal and non-fatal opioid poisoning (per 1000 patient years) in opioid dependent patients treated with methadone (MMT), buprenorphine (BUP) and naltrexone (NALT).

	Male			Female		
	MMT	BUP	NALT	MMT	BUP	NALT
Pre-treatment	13.6	19.3	9.6	28.2	33.0	40.4
Post-fatal	2.8	3.4	5.0*	2.0	1.8	1.6
Post-non-fatal	14.4	14.4	11.5	21.6	14.8	20.2

* $p < 0.05$.

Factors associated with risk of fatal opioid overdose

Univariate analysis found a significantly lower risk of fatal opioid overdose in female patients compared with males, with females dying at half the rate (Table 3). In terms of pre-treatment hospital admissions, an opioid overdose in the two years prior to treatment was associated with a significant increase of experiencing a fatal opioid overdose following the commencement of treatment ($p < 0.001$). Similarly, pre-treatment drug overdose, and cardiovascular admissions were also associated with increased mortality as a result of opioid overdoses. Examination of types of cardiovascular diseases associated with increased risk of opiate overdose, found admissions with a diagnosis of diseases of the veins, lymphatic vessels and lymph nodes (ICD-10: I80–89) were associated with a significant increase in risk (HR: 4.48, CI: 1.97–10.19, $p < 0.001$). In the multivariate model, only gender (HR: 0.53, CI: 0.34–0.82) and pre-treatment opioid overdose (HR: 4.46, CI: 2.45–8.11) were statistically significant.

Univariate analysis of post-treatment admissions, observed an increased risk of fatal opioid overdose in patients following an opioid overdose, a non-opioid drug overdose, intentional self-harm, mental health, cardiovascular and respiratory hospital admission. For cardiovascular admissions, increased incidence of fatal opiate overdoses was observed in patients with an admission for pulmonary heart disease and other diseases of the pulmonary circulation (ICD: I26–28) (HR: 2.82, CI: 1.14–6.75, $p = 0.025$), other forms of heart disease (excluding rhematic, ischaemic and pulmonary heart disease) (ICD: I30–52) (HR: 3.2, CI: 81.70–6.32, $p < 0.001$) and diseases of the veins, lymphatic vessels and lymph nodes (HR: 3.87, CI: 2.06–7.27, $p < 0.001$). For respiratory admissions, increased risk of fatal opiate overdose was associated

Table 4
Univariate hazard ratios associated with potential risk factors for opioid overdose following the commencement of treatment.

	Hazard ratio	Confidence interval	p-Value
Baseline variables			
Gender	0.55	0.36–0.85	0.007
Age of first treatment	1.00	0.98–1.02	0.765
Pre-treatment admission (2 years prior)			
Opioid overdose	4.16	2.29–7.57	0.000
Non-opioid drug overdose[a]	2.17	1.22–3.86	0.009
Attempted suicide	1.82	0.98–3.38	0.059
Mental health	1.46	0.88–2.41	0.142
Cardiovascular admission	2.42	1.07–5.51	0.035
Respiratory admission	1.71	0.75–3.88	0.202
Post treatment (TVC)			
Opioid overdose	7.71	4.99–11.91	0.000
Non-opioid drug overdose[a]	4.78	3.17–7.21	0.000
Attempted suicide	3.59	2.30–5.59	0.000
Mental health	2.99	2.02–4.43	0.000
Cardiovascular event	3.90	2.39–6.38	0.000
Respiratory event	3.13	1.90–5.15	0.000
Hepatitis C	2.38	0.87–6.50	0.091

TVC = time varying covariate.
[a] Includes opioid overdoses were non-opioid drugs were involved.

with admissions associated with acute lower respiratory infections (excluding influenza and pneumonia) (ICD: J20–22) (HR: 3.09, CI: 1.26–7.60, $p = 0.014$), other diseases of the upper respiratory tract (ICD: J30–39) (HR: 3.95, CI: 1.91–8.13, $p < 0.001$) and chronic lower respiratory disease (ICD: J40–47) (HR: 4.06, CI: 2.17–7.60, $p < 0.001$) (Table 4). In the multivariate model, gender (HR: 0.50, CI: 0.33–0.78), opioid poisoning (HR: 5.07, CI: 3.12–8.26), cardiovascular (HR: 2.32, CI: 1.38–3.91) and mental health hospitalisations (HR: 1.91, CI: 1.22–2.97) were significant predictors.

Discussion

Of the three treatments, buprenorphine appeared to be the safest in terms of both fatal and non-fatal opioid overdose. Compared with pre-treatment measures, rates of opioid poisoning hospitalisation decreased by 39.6% following induction onto buprenorphine. During induction, rates of non-fatal opioid overdoses were high compared with pre-treatment values but comparative to both methadone and naltrexone, however, unlike methadone, no fatal opioid overdoses were observed. Following the first 28 days, rates of non-fatal opioid overdoses were lower than both methadone and implant naltrexone patients and post treatment the three were comparable in terms of both fatal and non-fatal opioid overdoses. Buprenorphine's superiority to methadone in terms of opioid overdoses is most likely the result of methadone's increased ability to cause respiratory depression.

Implant naltrexone was also associated with positive opiate overdose outcomes. Although not statistically significant, following the commencement of treatment there was a 28.3% reduction in the rate of hospitalisation for opioid-poisoning. As per buprenorphine, while high rates of non-fatal opioid overdoses were observed in the first 28 days of treatment, no fatal opioid overdoses were observed. While on treatment, rates of both fatal and non-fatal opioid overdose were comparable to methadone, however once treatment had ceased, rates of non-fatal opioid overdose were lower in the naltrexone cohort. Unlike methadone and buprenorphine, naltrexone does not cause respiratory depression, in fact, it blocks the effects of other opioids which may induce respiratory depression. However, it is unclear why naltrexone did not perform as well as buprenorphine, with no evidence to suggest a difference in the type of opioid overdoses observed (i.e. difference in the frequency of co-diagnoses of intentional self-harm or non-opioid drug poisoning).

Methadone did not perform as well as buprenorphine or naltrexone, primarily as a result of very high rates of fatal opioid overdose in the first 28 days of treatment (14.1 deaths ptpy in methadone compared with 0 ptpy in both buprenorphine and implant naltrexone patients). Methadone had the smallest change in crude rates of hospital admission for opioid poisoning, with only 9.2% reduction. Similarly, rates of non-fatal opioid overdose were high compared with buprenorphine patients in the on treatment period, and higher than naltrexone patients following the cessation of treatment. High rates of fatal opioid overdose during induction onto methadone have been previously reported (Buster et al., 2002; Davoli et al., 2007; Degenhardt et al., 2009).

While male patients entering treatment looked similar in terms of pre-treatment opioid poisoning, female patients prior to commencement of naltrexone treatment had high rates of non-fatal opioid overdoses. However, following commencement of treatment, both naltrexone and buprenorphine, rates of opioid overdose were approximately halved in female patients, while rates in male patients entering any treatment and female patients on methadone remained unchanged. Gender differences in the effectiveness of naltrexone have been previously observed. Herbeck et al. (2016), found women treated with extended release naltrexone for alcohol and opioid use disorders had high rates of adverse events, but significantly greater reduction in craving scores compared with men. Such a difference in gender response may be attributable to gender based difference in bioavailability, distribution, metabolism and elimination of the naltrexone or potentially a difference in sensitivity of the opioid pathways (Pettinati et al., 2008).

The first 28 days following the commencement of treatment was shown to be a highly risky period in terms of opioid overdose, particularly in patients treated with methadone where fatalities were high. However, regardless of treatment, the first month of treatment should be viewed as an increased risk period for opioid poisoning in stabilising illicit opioid users, with steps taken to identify and intervene with high risk individuals.

Both fatal and non-fatal opioid overdoses were commonly associated with the use of other non-opioid drugs (67.3% and 55.4% respectively). The presence of non-opioid drugs is common in opioid overdoses in Australia and similarly in a review of 200 opioid overdoses, two or more different drugs were found in 71% of autopsies, with alcohol found in 45% and benzodiazepines in 26%. Further investigation is required to examine what drugs were present in this cohort and at what concentrations.

While intentional self-harm was a common co-diagnosis in non-fatal opioid overdoses, occurring in almost half of the opioid overdose admissions (48.0%), it was only listed as a co-diagnosis in 6.3% of fatal opioid overdoses. Intentional self-harm may have been underreported in fatal overdoses and may have been easily mistaken for an unintentional overdose, particularly as blood morphine levels are not accurate indicators of intent (Darke et al., 2007, 2000; Meissner et al., 2002).

Respiratory and cardiovascular diagnoses were commonly associated with opioid overdose. Respiratory co-diagnosis was most prevalent in fatal opioid overdose in methadone patients, particularly while on treatment. This may be attributed to methadone's ability to depress respiratory function.

Hospitalisation for an opioid overdose in the two years prior to treatment and following initial treatment, were associated with a significant increase in the risk of dying of an opioid overdose. As such, strategies to reduce the rates of fatal opioid overdoses could be implemented by both drug and alcohol treatment services at the commencement of treatment and at hospitals following admission

for an opioid overdose. This is in keeping with previous research by StoovÉ, Dietze, and Jolley (2009) that found individuals who experience more than two opioid overdoses attended by an ambulance were at a more than a 7 fold increase in risk of dying of an opioid overdose compared with individuals who experience just a single opioid overdose (StoovÉ et al., 2009).

Unsurprisingly, as described previously, male patients were at a high risk of fatal opioid poisoning, with males dying at twice the rate of female patients in both models. Such has traditionally been associated with increased risky behaviour in males (Cornish, Macleod, Strang, Vickerman, & Hickman, 2010; Degenhardt et al., 2011; Thom, 2003). Interestingly, post treatment hospital admission with a cardiovascular diagnosis was associated with a significant increase in fatal opioid overdose. The increase was associated with diseases of the veins, lymphatic vessels and lymph nodes, which includes diseases such as phlebitis and thrombophlebitis, all of which are common in intravenous drug users (Briggs, McKerron, Souhami, Taylor, & Andrews, 1967; Mackenzie, Laing, Douglas, Greaves, & Smith, 2000). It is probable that the occurrence of such admissions are more likely in patients who are currently using drugs intravenously, and thus have a greater risk of opiate poisoning than patients using other routes or not using (Warner-Smith, Lynskey, Darke, & Hall, 2000).

Opioid dependence has been associated with high rates of cardiovascular disease and cardiovascular abnormalities in both illicit opioid users and those on opioid pharmacotherapies such as methadone (Dressler & Roberts, 1989; Lipski, Stimmel, & Donoso, 1973). This represents a major cause of death in opioid dependent patients, accounting for between 1.0 to 18.9% of all deaths, or approximately 0.9 deaths per 1000 patient years (ptpy) (Degenhardt et al., 2011). Prior hospitalisations with cardiovascular diagnoses may be indicative of cardiovascular damage or susceptibility, making a patient less resilient to opioid overdoses.

Following the commencement of treatment, hospitalisation for a mental health event was also positively associated with an increased risk of opioid poisoning. One possible explanation may be that patients with a mental health associated hospital admission may be more likely to attempt suicide using opioids or be more likely to combine opioids with other illicit or licit drugs.

Rates of fatal opioid overdose were not significantly different in patients diagnosed with HCV compared with those not diagnosed with HCV. While HCV is a common cause of hepatic damage in intravenous drug users, the effects of HCV are highly variable, with most patients initially experiencing minimal or no symptoms; significant liver impairment often takes decades to develop (Marcellin, Asselah, & Boyer, 2002).

Limitations

Rates of non-fatal opioid poisoning were limited to those requiring hospital admission, and thus did not include opioid poisoning that required only emergency department attendance, or those who did not seek medical assistance. As such, ratios of fatal to non-fatal opioid overdoses in this study were much lower than in previous studies. For example, in a study by Darke, Mattick, and Degenhardt (2003) ratio of fatal to non-fatal opioid overdoses were reported as 1:31 based on self-reported accounts of non-fatal opioid overdoses (Darke et al., 2003). Similarly, in a prospective study, Neale (2003), using self-reported opioid overdoses, calculated a ratio of fatal to non-fatal overdose of 1:26 (Neale, 2003). Additionally, as the study used only state wide datasets, both fatal and non-fatal opioid overdoses that occurred interstate or overseas may not have been included in the study.

The study has a naturalistic design, with patients having self-selected their own treatment. The lack of randomisation may result in some bias, with certain patient groups potentially being more likely to select certain treatments. There is some evidence of this in the rates of pre-treatment non-fatal opioid overdoses in female patients, with naltrexone women having 40.8 admission per 1000 patient years compared with 28.2 in methadone and 33.0 in buprenorphine treated women.

Conclusions

Overall, rates of fatal and non-fatal opioid overdose were not significantly different in patients treated with methadone, buprenorphine or implant naltrexone. Buprenorphine and naltrexone were efficient in reducing non-fatal opioid admission in female patients, while rates remained relatively unchanged in males treated with any of the three treatments. Non-opioid drug poisoning was the most common diagnoses associated with both fatal and fatal opiate overdoses. Hospital data could be used to identify opioid dependent patients at a high risk of opioid overdose death.

Acknowledgements

The research team would like to acknowledge the support of the Data Linkage Branch and the data custodians for linking the data and the Western Australian Department of Health data custodians for providing the data. Funding for this study was provided by the State Health Research Advisory Council (SHRAC) via a Research Translation Project Grant. SHRAC was not involved in the study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

Conflict of interest

The authors declare that they have no conflict of interest.

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