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Research paper

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

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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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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