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The impact of blood-borne viruses on cause-specific mortality among opioid dependent people: An Australian population-based cohort study

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ABSTRACT

Background: Blood-borne viruses (BBV) are prevalent among people with opioid dependence but their association with cause-specific mortality has not been examined at the population-level.
Methods: We formed a population-based cohort of 29,571 opioid substitution therapy (OST) registrants in New South Wales, Australia, 1993–2007. We ascertained notifications of infection and death by record linkage between the Pharmaceutical Drugs of Addiction System (OST data), registers of hepatitis C (HCV), hepatitis B (HBV) and human immunodeficiency virus (HIV) diagnoses, and the National Death Index. We used competing risks regression to quantify associations between notification for BBV infection and causes of death. BBV status, age, year, OST status, and OST episodes were modelled as time-dependent covariates; sex was a fixed covariate.
Results: OST registrants notified with HCV infection were more likely to die from accidental overdose (sub-distribution hazard ratio, 95% Confidence Interval: 1.7, 1.5–2.0), cancer (2.0, 1.3–3.2) and unintentional injury (1.4, 1.0–2.0). HBV notification was associated with a higher hazard of mortality due to unintentional injury (2.1, 1.1–3.9), cancer (2.8, 1.5–5.5), and liver disease (2.1, 1.0–4.3). Liver-related mortality was higher among those notified with HIV only (11, 2.5–50), HCV only (5.9, 3.2–11) and both HIV and HCV (15, 3.2–66). Registrants with an HIV notification had a higher hazard of cardiovascular-related mortality (4.0, 1.6–9.9).
Conclusions: Among OST registrants, BBVs are a direct cause of death and also a marker of behaviours that can result in unintended death. Ongoing and enhanced BBV prevention strategies and treatment, together with targeted education strategies to reduce risk, are justified.

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1. Introduction

Systematic reviews of cohort studies suggest that opioid-dependent people may have a 15-fold increased risk of death compared to the general population, although there is considerable geographical variation in the extent of this increase (Degenhardt et al., 2011; Mathers et al., 2013). Accidental drug overdose, suicide, and unintentional injury are leading causes of death among this group in high-income countries (Degenhardt et al., 2011), with liver disease emerging as an increasingly important cause in recent years (Gibson et al., 2011; Larney et al., 2013). Opioid substitution therapy (OST) halves this excess risk (Degenhardt et al., 2011; Mathers et al., 2013), whilst also reducing illicit drug use, reducing the incidence of human immunodeficiency virus (HIV) and possibly hepatitis C (HCV) infection, and improving the physical and mental health of dependent opioid users (Gowing et al., 2008; MacArthur et al., 2014; Mattick et al., 2009; Ward et al., 1999; White et al., 2014).

Most heroin users have a history of injecting drug use (Ross et al., 2005), making them susceptible to infection with blood-borne viruses (BBVs), specifically HCV, hepatitis B (HBV) and HIV, through shared needles and syringes. Infection prevalence estimates for HCV, HBV and HIV among Australian injectors, for example, are 50–60% (Nelson et al., 2011), 2.7–5% (Nelson et al., 2011), and 1.5% (Mathers et al., 2008) respectively. Whilst chronic infection with these agents is known to increase the risk of death, their contribution to cause-specific mortality among opioid-dependent people is uncertain (Larney et al., 2013; McDonald et al., 2011). Prior studies of opioid-dependent people with data on BBV infection status have been based on relatively small, clinic-based cohorts (Brugal et al., 2005; Eskild et al., 1993; Evans et al., 2012; Goedert et al., 1995; Huang and Lee, 2013; Manfredi et al., 2006; Miller et al., 2007; Muga et al., 2014; Tyndall et al., 2001; Vlahov et al., 2008) or community-based cohorts of individuals tested for HCV (Grebely et al., 2011; McDonald et al., 2009), which may not be representative of the opioid-dependent population. Furthermore, some studies only assessed BBV status at the beginning or end of follow-up (Brugal et al., 2005; Muga et al., 2014), most evaluated only all-cause mortality and/or a single cause of death (Brugal et al., 2005; Cao et al., 2013; Eskild et al., 1993; Evans et al., 2012; Grebely et al., 2011; Huang and Lee, 2013; Manfredi et al., 2006; Miller et al., 2007; Muga et al., 2014; Tyndall et al., 2001; Vlahov et al., 2008), and none controlled for competing risks of death, despite the very high rate of mortality from causes that share risk factors. No prior study examining cause-specific mortality in opioid-dependent people incorporated longitudinal data on HCV, HBV and HIV infection status.

We examined cause-specific mortality in a cohort of all opioid-dependent people who entered OST in New South Wales (NSW), Australia over a 15-year period. Our aim was to quantify the association between longitudinal HCV, HBV and HIV infection status and cause-specific mortality whilst controlling for competing risks of death from other causes.

2. Material and methods

2.1. Study population

We formed a population-based cohort using record linkage between administrative data sets. Our study population was persons aged 16 years and over registered on the Pharmaceutical Drugs of Addiction System (PHDAS) in NSW, Australia, 1993–2007 (n = 32,104). The PHDAS records all NSW Department of Health authorised opioid-dependent people treated with methadone or buprenorphine, including the start and finish date of each treatment episode. As proof of patient identity is required to be shown to the prescribing doctor before a prescription can be issued, the accuracy of this information in the dataset is high. The eligibility criteria for OST in NSW have not changed over time (Van Buskirk and Burns, 2013). There is no requirement for cessation of drug use (although it is actively discouraged). The only change in OST provision over time was the introduction of buprenorphine in 2001.

We excluded registrants if information required for record linkage was incomplete (n = 1), if the resultant linked data were inconsistent (n = 28, 0.1%), or if they resided interstate (n = 2462, 7.7%). We also excluded registrants with an unknown underlying cause of death (n = 42, 0.1%).

2.2. Data collection

In Australia, it is a statutory requirement that all deaths and HIV, HCV, and HBV infections are reported to government agencies. In our cohort the date and underlying cause of death were ascertained by record linkage with the National Death Index (1980+). Causes of death were coded from death certificates at the Australian Bureau of Statistics using International Classification of Diseases (ICD) version 9 for deaths in 1993–1996 and ICD-10 for deaths in 1997–2007. We ascertained notifications of incident HIV infections by linkage with the National HIV Database (1985+) and the National AIDS Register (1982+). Linkage with the NSW Health Notifiable Conditions Information Management System (1993+) identified incident HBV and HCV infection notifications. These notifications are based on detection of HBV surface antigen or HBV DNA and anti-HCV antibody or HCV RNA, respectively. Serological evidence of HBV and HCV infection was thus only available for NSW residents.

The registrant's full name, sex, date of birth, date of death, and state of residence were used for the death, HBV and HCV record linkage. For the HIV/AIDS linkage the registrant's name was reduced to the first two letters of their first and last name, corresponding to the restricted named information on HIV/AIDS notifications. The death, HBV and HCV record linkage used probabilistic matching techniques whilst the HIV/AIDS linkage used deterministic methods due to the availability of less identifying information. The study was reviewed and approved by all relevant ethics committees.

2.3. Statistical analysis

The outcome of interest was the underlying cause of death; we examined the six major causes for this population, namely accidental drug-induced (overdose), unintentional injuries (motor vehicle and transport accidents, falls, fires/burns, drownings and violence), suicide, cardiovascular disease, cancer and liver disease. We categorised deaths according to a toolkit (Randall et al., 2009), with one exception; we excluded accidental poisonings (predominantly overdoses) from unintentional injuries.

We calculated person-years of follow up from entry into the first OST program (episode) until the date of transfer to interstate OST (n = 2297), death, or the end of the study period (1 January 2008), whichever occurred first. When classifying the number of OST episodes, if there were fewer than 7 days between the end date of one episode and the start date of the next episode, then we considered it a continuous episode (Degenhardt et al., 2005a).

We used Fine and Gray competing risks regression models to investigate within-cohort risk factors associated with specific causes of death accounting for mortality due to other causes from which estimates of the subdistribution hazards ratio (SHR) and 95% confidence interval (CI) were obtained (Fine and Gray, 1999). The competing risk approach is necessary because OST registrants are at increased risk of more than one cause of death, several of which share risk factors (Odegard et al., 2007). With this method, individuals who die from a cause other than the one under study remain in the risk set, and the subdistribution hazards estimate the 'real world' probabilities of death due to specific causes.

We modelled date of HBV, HCV and HIV notification (diagnosis), age, calendar year of follow up, treatment status (in/out of OST), and number of OST episodes as time-dependent covariates and sex as a fixed covariate. For each cause of death we examined bivariable associations and then built a final multivariable model using the purposeful selection of covariates method (Hosmer and Lemeshow, 1999). Variables were retained in the model if $p < 0.05$ or if they confounded the association for one or more other variables. We assessed interactions between HCV and HIV, as well as between HCV and HBV, and retained them for assessment in multivariable models if $p < 0.20$. We verified the proportional subdistribution hazards assumption for each covariate. We performed all analyses using SAS 9.1 (SAS Institute, Cary, NC, USA) and STATA 11.2 (Stata Corporation, College Station, Texas, USA).

3. Results

Our eligible cohort comprised 29,571 people who had received OST for opioid dependence in 1993–2007. The median age at OST entry was 26 years (interquartile range [IQR] 22–33) and 69% were men (Table 1). The median interval between first OST episode and either death or the end of follow-up was 7.3 years (IQR 3.7–10.6), with a total of 212,784 person-years of follow up. The median cumulative time on OST was 2.1 years (IQR 0.5–5.2), the median time off OST was 1.7 years (IQR 0.5–3.7), and the median number of treatment episodes was 2 (IQR 1–3). By the end of follow-up, 52%