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The contributions of viral hepatitis and alcohol to liver-related deaths in opioid-dependent people

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ABSTRACT

Background: Mortality rates are elevated among heroin-dependent populations compared to the general population. Liver disease is emerging as an important contributor to mortality as the heroin-dependent population ages. Two major risk factors for liver disease are hepatitis C virus infection and chronic heavy alcohol use. Both of these are highly prevalent among heroin dependent people, but their relative contribution to liver-related mortality is poorly understood.

Methods: Data recording all prescriptions of opioid substitution treatment in New South Wales, Australia, 1997–2005, were linked to the National Death Index. Crude and standardised mortality rates and standardised mortality ratios were calculated for liver-related and other major causes of death. Frequency counts were obtained for viral hepatitis and alcohol mentions in underlying liver deaths.

Results: There were 208 underlying liver deaths for a CMR of 72.4 per 100,000 py (95% CI 62.9, 82.9), and liver deaths occurred at 9.8 times the general population rate (95% CI 8.5, 11.2). There were increases in liver-related mortality over time. Viral hepatitis was mentioned in three-quarters ($n = 156$, 76%), and alcohol in 43% ($n = 90$) of underlying liver deaths.

Conclusions: Liver-related deaths were shown to be increasing in this heroin-dependent population, and the majority of these deaths involved chronic viral hepatitis infection. Increased uptake of treatment for hepatitis C virus infection is crucial to reducing the burden of liver-related mortality in this population. Hepatitis B vaccination, and screening of OST patients for alcohol use disorders and delivery of brief interventions as clinically indicated may also be of benefit.

1. Introduction

Mortality rates are elevated among heroin-dependent populations compared to the general population. The most frequent causes of death among this group are drug overdose, suicide, traumatic injuries and, in regions with high HIV prevalence among people who inject drugs (PWID), AIDS (Degenhardt et al., 2011).

In the developed world, the heroin-dependent population is ageing (Burns et al., 2009; EMCDDA, 2010), and AIDS deaths are declining as a result of improved treatment for HIV infection (Manfredi et al., 2006; Pavarin, 2008). These trends may result in changes in mortality rates and the relative contributions of various causes of death to overall mortality (EMCDDA, 2010). One source of mortality that may be of increasing importance is liver disease. In a cohort of heroin users who entered opioid substitution treatment (OST) in Australia between 1980 and 1985, liver-related deaths accounted for 17% of cohort mortality, and by 2005, liver diseases were a more frequent underlying (primary) cause of death than drug overdose. Liver diseases were also frequently noted as a contributing (secondary) cause of death (Gibson et al., 2011).

Two major risk factors for liver disease are viral hepatitis and heavy alcohol use, both of which are elevated among heroin users compared to the general population. Viral hepatitis is elevated due to the high prevalence of injection as a route of heroin administration; in New South Wales (NSW), the setting of this study, around 95% of heroin users have a history of injecting drug use (Ross et al., 2005) and 98% of PWID drugs have injected heroin (Phillips and Burns, 2012). An estimated two-thirds of PWID globally are hepatitis C antibody (anti-HCV) positive, and approximately 8% are hepatitis B surface antigen (HBsAg) positive (Nelson et al., 2011). In a recent Australian cohort of PWID, 39% were anti-HCV positive, and 4% were HBsAg positive (White et al., 2012). Chronic viral hepatitis is associated with severe liver disease including cirrhosis and hepatocellular carcinoma (Dore et al., 2002; Freeman et al., 2001).

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These potentially fatal sequelae of chronic infection do not emerge until several decades after initial virus exposure (Dore et al., 2002).

Prevalence of alcohol dependence among heroin using cohorts has been reported as 40–65% (Darke and Ross, 1997; Feldman et al., 2011; Shand et al., 2011). As with chronic hepatitis B and C infection, chronic heavy alcohol use may lead to significant liver morbidity (Altamirano and Bataller, 2011). The presence of multiple risk factors for cirrhosis, such as viral hepatitis infection with comorbid alcohol dependence, increases the likelihood and speed of progression to severe liver disease (Freeman et al., 2001; Walter et al., 2011).

The relative contribution of viral hepatitis and alcohol to liver-related mortality among heroin users is poorly understood. In a Scottish cohort of PWID, alcohol use was a more important factor in liver disease progression than HCV infection (McDonald et al., 2011); however, in the Australian treatment cohort cited above, viral hepatitis was the underlying cause of death in 45% of liver-related deaths, compared to 17% of liver-related deaths with an underlying cause of alcoholic liver disease (Gibson et al., 2011). This latter analysis did not take into account those liver-related deaths where viral hepatitis and/or alcohol use (as distinct from alcoholic liver disease) were implicated as contributing causes. It is possible for a death to be assigned an underlying cause of, for example, cirrhosis, with viral hepatitis and/or alcohol use noted as contributing causes (and vice versa). Examining both underlying and contributing causes of death thus provides a more complete understanding of how viral hepatitis and alcohol contribute to liver-related mortality. Using a larger, later cohort from the same treatment program as in Gibson et al. (2011), this study aimed to quantify liver-related mortality in a heroin dependent population, and examine the extent to which viral hepatitis and alcohol are implicated in liver-related mortality among heroin users.

2. Method

2.1. Study population

New South Wales (NSW) is the most populous state in Australia and has the largest OST program in the country, with over 40,000 individuals receiving treatment since 1985 (Burns et al., 2009). The study population comprised all patients (n = 20,896) who registered for OST between 1997 and 2005.

2.2. Data sources, linkage and definitions

The Pharmaceutical Drugs of Addiction System (PHDAS) contains details of all people entering OST in NSW. PHDAS records for the calendar years 1997–2005 were probabilistically linked to the National Death Index (NDI), which records all deaths in Australia. Linkage was performed by staff of the Australian Institute of Health and Welfare (AIHW), the data custodian of the NDI, using in-house software. Multiple passes were run, using identifying information including full name, aliases, date of birth, sex, and date and state of last contact. Exact and 'good' matches were accepted as links. The 'good' matches were decided based on AIHW-recommended weight cut-offs for different passes.

Deaths were coded using the International Classification of Diseases version 10 (ICD-10) and up to 18 contributing causes of death could be coded in addition to the underlying cause of death. Liver-related deaths were defined as those with an underlying cause of death of viral hepatitis (B15–B19, B94.2), liver disease (K70–K77) or liver cancer (C22) (Randall et al., 2009). Other selected underlying causes of death, reported for comparison purposes, were defined using ICD-10 codes as in Randall et al. (2009).

2.3. Data analysis

All analyses were conducted using SAS 9.3 (SAS Institute, 2010). Person-years accrued from the date of first treatment registration until death or 31 December 2005, whichever occurred first. Crude mortality rates (CMRs) for underlying liver deaths and other commonly reported causes of death for opioid-dependent populations were calculated from the number of deaths and number of person-years of follow-up. Directly standardised mortality rates were calculated for underlying liver deaths, standardised to the average age and sex profile for the cohort. Indirectly standardised mortality ratios (SMRs) were calculated using the age-, sex- and year-specific mortality rates for the NSW population. Poisson confidence limits were calculated for all rates and ratios.

Temporal trends in the number of underlying liver deaths, underlying liver deaths as a proportion of all deaths, the median age of underlying liver decedents and crude and standardised underlying liver mortality rates were examined. Significance of temporal trends in the proportion of underlying liver deaths and age of liver decedents was assessed using the Cochran–Armitage test for trend.

To examine the relative contributions of viral hepatitis and alcohol use to liver-related deaths, both underlying and contributing causes of death were considered. This allowed us to identify liver deaths with an underlying cause of viral hepatitis or alcoholic liver disease, as well as deaths that were assigned an underlying cause of death of liver cancer or cirrhosis, but to which viral hepatitis or alcohol were acknowledged as contributing factors. Underlying liver deaths were categorised into four mutually exclusive categories: deaths with viral hepatitis (B15-B19, B94.2) as an underlying or contributing cause and no alcohol-related causes; deaths with alcohol-related codes (E24.4, F10, G31.2, G62.1, G72.1, I42.6, K29.2, K70, K86.0, R78.0, X45, X65, Y15) as an underlying or contributing cause and no viral hepatitis causes; deaths in which with both viral hepatitis and alcohol were implicated; and deaths with neither of these factors. An area-proportional Venn diagram was constructed using Venn Diagram Plotter, available from http://omics.pnl.gov/software/.

2.4. Ethical approval

Ethical approval for the study was obtained from all relevant institutional human research ethics committees. Consent requirements were waived by the committees as it was impractical to seek consent from the large number of participants, the researchers did not have access to contact details, a significant proportion of the population would be deceased, and consent would introduce selection bias to the study.

3. Results

3.1. Major causes of death

The study cohort included 20,896 people, of whom just over two-thirds were male (n = 14,122; 68%); the median age on entering the cohort was 27 years. There were 287,330 person-years of follow-up and 2619 deaths between 1997 and 2005, for an all-cause crude mortality rate (CMR) of 911.5 per 100,000 person-years (py; 95% CI 876.9, 947.1). The all-cause standardised mortality ratio (SMR) was 5.3 (95% CI 5.1, 5.5) (Table 1).

Drug-induced deaths comprised half (n = 1290; 49%) of all deaths and occurred at 22 times the rate seen in the general population (SMR 21.9, 95% CI 20.7, 23.1; Table 1). Traumatic injuries (n = 633; 24%) and suicides (n = 330; 13%) accounted for the bulk of