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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

Table 1
Crude mortality rates, standardised mortality ratios and liver morbidity as a contributing cause of death for selected underlying causes of death among New South Wales opioid substitution treatment participants, 1997–2005 (n = 20,896).

Underlying cause of death	*N* deaths	CMR per 100,000 person-years (95% CI)	SMR (95% CI)*	*N* (%) with liver morbidity as a contributing cause
All deaths	2619	911.5 (876.9, 947.1)	5.3 (5.1, 5.5)	536 (20)
Male	1968	1056.6 (1010.4, 1104.3)	4.9 (4.7, 5.1)	401 (20)
Female	651	644.1 (595.6, 695.5)	6.8 (6.3, 7.3)	135 (21)
Liver	208	72.4 (62.9, 82.9)	9.8 (8.5, 11.2)	164 (79)
Male	164	88.1 (75.1, 102.6)	9.2 (7.8, 10.7)	128 (78)
Female	44	43.5 (31.6, 58.4)	13.4 (9.8, 18.0)	36 (82)
Drug induced	1290	449.0 (424.8, 474.1)	21.9 (20.7, 23.1)	181 (14)
Male	974	522.9 (490.6, 556.8)	19.4 (18.2, 20.6)	136 (14)
Female	316	312.6 (279.1, 349.1)	36.0 (32.1, 40.1)	45 (14)
Injury	633	220.3 (203.5, 238.2)	3.8 (3.5, 4.1)	58 (9)
Male	490	263.1 (240.3, 287.4)	3.3 (3.1, 3.7)	46 (9)
Female	143	141.5 (119.2, 166.7)	7.1 (6.0, 8.4)	12 (8)
HIV/AIDS	45	15.7 (11.4, 21.0)	5.3 (3.9, 7.1)	7 (16)
Male	36	19.3 (13.5, 26.8)	4.4 (3.1, 6.1)	6 (17)
Female	9	8.9 (4.1, 16.9)	36.2 (16.6, 68.7)	1 (11)
Suicide	330	114.9 (102.8, 127.9)	4.2 (3.7, 4.6)	26 (8)
Male	258	138.5 (122.1, 156.5)	3.7 (3.2, 4.2)	19 (7)
Female	72	71.2 (55.7, 89.7)	8.1 (6.3, 10.2)	7 (10)
Cancer	181	63.0 (54.2, 72.9)	1.7 (1.4, 1.9)	54 (30)
Male	128	68.7 (57.3, 81.7)	1.8 (1.5, 2.1)	40 (31)
Female	53	52.4 (39.3, 68.6)	1.4 (1.1, 1.9)	14 (26)
Cardiovascular disease	170	59.2 (50.6, 68.8)	2.2 (1.9, 2.6)	42 (25)
Male	114	61.2 (50.5, 73.5)	1.8 (1.5, 2.1)	28 (25)
Female	56	55.4 (41.9, 71.9)	4.7 (3.6, 6.1)	14 (25)

CMR, crude mortality rate; SMR, standardised mortality ratio (standardised by sex, age and calendar year).
* All significantly elevated at 95% confidence level.

remaining deaths, with SMRs of 3.8 (95% CI 3.5, 4.1) and 4.2 (95% CI 3.7, 4.6) respectively. AIDS deaths were uncommon (n = 45; 2%), but were still significantly elevated compared to the general population (SMR 5.3; 95% CI 3.9, 7.1).

There were 208 decedents with a liver-related underlying cause of death, comprising 8% of all deaths in the cohort. The CMR for liver deaths was 72.4 per 100,000 py (95% CI 62.9, 82.9) and liver deaths occurred at 9.8 times the rate seen in the general population (95% CI 8.5, 11.2) (Table 1). Underlying liver deaths were more common among men (CMR: 88.1 per 100,000 py; 95% CI: 75.1, 102.6) than women (CMR: 43.5 per 100,000 py; 95% CI: 31.6, 58.4); however, excess mortality was higher for women (SMR: 13.4; 95% CI: 9.8, 18.0) than men (SMR: 9.2; 95% CI: 7.8, 10.7).

Liver diseases were noted as contributing causes in 20% (n = 536) of deaths (Table 1); in total, liver disease was an underlying or contributing cause in 22% (n = 580) of deaths. The crude mortality rate associated with liver disease as an underlying or contributing cause of death was 201.9 per 100,000 py (95% CI 185.8, 219.0). Nearly one-third of underlying cancer deaths (30%) and one-quarter of underlying cardiovascular deaths (25%) mentioned liver disease as a contributing cause, but it was less frequently noted in injury (9%) and suicide deaths (8%; Table 1).

3.2. Temporal trends in underlying liver deaths

Temporal trends in underlying liver deaths are shown in Table 2. Underlying liver deaths comprised an increasing proportion of cohort deaths over time, from 4.5% of deaths occurring in 1997–1999 to 11.9% in 2003–2005 (Cochrane–Armitage trend test $p < .0001$). The crude mortality rate of underlying liver deaths increased over time, from 52.4 per 100,000 py (95% CI 37.4, 71.4) in 1997–1999 to 93.2 per 100,000 py (95% CI 76.3, 112.7) in 2003–2005. The age- and sex-standardised mortality rate increased from 64.3 per 100,000 py (95% CI 44.4, 89.6) in 1997–1999 to 78.2 per 100,000 py (95% CI 63.7, 94.9) in 2003–2005. Excess mortality in comparison to the general population also increased over time (Table 2).

3.3. Viral hepatitis and alcohol in underlying liver deaths

Viral hepatitis was mentioned in three-quarters of underlying liver deaths (n = 156; 76%). Alcoholic liver disease was specifically mentioned in 32% of underlying liver deaths (n = 67); more generally, alcohol was mentioned in 43% (n = 90) of underlying liver deaths. When examined in terms of mutually exclusive risk

Table 2
Temporal trends in underlying liver-related mortality in New South Wales opioid substitution participants, 1997–2005 (n = 208).

Year period	*N* liver deaths	% of all deaths^	Median age of liver decedents, years (range)^	CMR per 100,000py (95% CI)	Age- and sex-standardised mortality rate per 100,000 py (95% CI)	SMR (95% CI)
1997–1999	40	4.5	42 (29–50)	52.4 (37.4, 71.4)	64.3 (44.4, 89.6)	10.3 (7.4, 14.0)
2000–2002	62	7.4	44 (32–55)	63.8 (48.9, 81.7)	66.6 (51.0, 85.4)	12.1 (9.3, 15.6)
2003–2005	106	11.9	46 (26–58)	93.2 (76.3, 112.7)	78.2 (63.7, 94.9)	12.3 (10.1, 14.9)

py, person-years; CMR, crude mortality rate; SMR, standardised mortality ratio (standardised to age, sex and calendar year).
^ Cochran-Armitage trend test $p < .0001$.

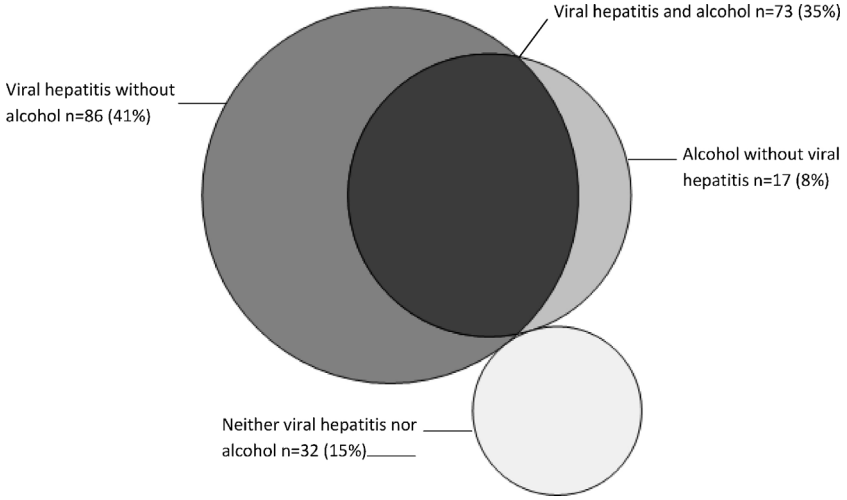

Fig. 1. Viral hepatitis and alcohol involvement in underlying liver deaths among New South Wales opioid substitution treatment participants, 1997–2005 ($n = 208$).

categories, the most common risk category was viral hepatitis without alcohol, which was mentioned in 41% ($n = 86$) of liver decedents. A combination of viral hepatitis and alcohol was mentioned in one-third ($n = 73$; 35%) of underlying liver deaths. Very few underlying liver deaths were attributable to alcohol without viral hepatitis ($n = 17$; 8%; Fig. 1).

4. Discussion

This study examined the contribution of liver diseases to mortality among a large cohort of people entering treatment for heroin dependence. The all-cause CMR was 911.5 per 100,000 py (95% CI 876.9, 947.1), similar to that reported for other Australian cohorts (Gibson et al., 2011; Stoove et al., 2008). Overall, deaths occurred at 5.3 times the rate of the general NSW population (95% CI 5.1, 5.5). The underlying liver CMR was 72.4 per 100,000py (95% CI 62.9, 82.9 per 100,000 py), less than the pooled CMR of 160 liver-related deaths per 100,000 py reported in a recent meta-analysis (Degenhardt et al., 2011), but still significantly elevated compared to the general population (SMR 9.8, 95% CI 8.5, 11.2). In keeping with other studies of mortality among opioid dependent populations, male participants had higher liver-related mortality rates than female participants; however, excess liver-related mortality was greater among women. These findings reflect general sex differences in mortality (Degenhardt et al., 2011).

Liver diseases were noted as underlying or contributing to one in five deaths occurring 1997–2005. Liver diseases were most commonly seen as contributing causes in those deaths with an underlying cause of cancer and cardiovascular disease, perhaps reflecting the role of shared risk factors and ageing in all three disease types. Analysis of temporal trends revealed increases in liver mortality over time in terms of absolute numbers and mortality rates. Viral hepatitis was implicated in three-quarters, and alcohol in just less than one half, of underlying liver deaths. Just over a third of underlying liver deaths included a combination of these factors.

There are clear clinical implications of this study. Liver-related deaths were shown to be increasing among heroin users, and the majority of these deaths involved chronic viral hepatitis infection. Given the epidemiology of viral hepatitis in this population (Ramasamy et al., 2010; White et al., 2012), it can be assumed that this is primarily through infection with HCV. HCV infection is treatable, but treatment uptake among PWID (who constitute the overwhelming majority of HCV cases) is extremely low (Gidding et al., 2009; World Health Organization, 2010). Barriers to treatment at the patient level include lack of awareness of treatment options; lack of symptoms; and concern about treatment side effects (Grebely et al., 2008). Clinicians can be reluctant to commence HCV treatment with patients who are actively injecting drugs (Higgs et al., 2011), despite evidence of good treatment adherence (Grebely et al., 2011) and response (Dore et al., 2010; Hellard et al., 2009) among PWID. Addressing these barriers and increasing treatment uptake among HCV-infected PWID is critical to reducing the severe and potentially fatal sequelae of chronic HCV. In addition to reducing the burden of disease associated with chronic HCV, higher treatment rates would result in significantly reduced HCV transmission among PWID (Martin et al., 2011; Vickerman et al., 2011).

Although HCV is likely the dominant form of viral hepatitis in this population, HBV is also present. In addition to being a risk factor for liver disease in itself, HBV/HCV co-infection increases the likelihood of disease progression and poor treatment outcomes (Donato et al., 1998; Weltman et al., 1995). HBV vaccination is a safe and effective measure for preventing primary and co-morbid infection, and should be offered to all PWID (Australian Government Department of Health and Ageing, 2008).

The role of alcohol in contributing to liver morbidity and mortality in this population should not be overlooked. There may be benefits to screening OST patients for alcohol use disorders and delivering brief interventions when indicated (Darker et al., 2012; Feldman et al., 2011). Addressing alcohol use may also be pertinent to reducing overdose risk, particularly for those prescribed buprenorphine (Häkkinen et al., 2012).

4.1. Limitations

This study used routinely collected datasets that were not designed for research purposes. Datasets were linked probabilistically; hence the quality of the linkage was dependent on the quality of identifiers recorded in each dataset. The quality of information in the PHDAS is considered to be high, as a patient must be identified by the prescribing doctor before being enrolled in the opioid treatment program (Burns et al., 2009; Randall et al., 2011). Information in the NDI is received from the Registry of Births, Deaths and Marriages in each Australian state and territory and there is no way to confirm the correctness and completeness of this data (Australian Institute of Health and Welfare, 2012). We are, however, confident of the accuracy of the data linkage given the similarity in overall mortality to another Australian cohort of PWID (Stoove et al., 2008).

Using routinely collected data, we were unable to examine specific exposures or potential confounders of liver-related mortality. For example, we were unable to determine the proportion of the cohort that was born in countries where HBV is endemic, or whether OST exposure had any impact on entry to care for viral hepatitis.

It should also be noted that the data presented here relate to opioid-dependent people seeking treatment. Whether a person commenced treatment or was retained in treatment was not relevant to our study, as we were analysing treatment effects on mortality. Opioid-dependent persons who have not sought OST may have a different clinical profile from those who have sought or are in OST. We are, however, confident that our cohort is reasonably representative of all opioid users in NSW; sentinel surveillance studies of PWID (98% of whom have a history of heroin use) suggest that half are in opioid substitution treatment at a specific point in time, and 80% report a history of OST (Phillips and Burns, 2012).

4.2. Conclusion

This follow-up of a large heroin-dependent cohort allowed for detailed analysis of underlying liver deaths. Liver-related mortality is increasing in the ageing heroin-dependent population as the sequelae of HCV infection acquired several decades ago begin to manifest. Without greatly increased HCV treatment uptake, liver mortality can be expected to increase into the future.

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Contributors

SL designed the study with input from LD, DR and AG. SL undertook the data analysis, adapting programs written by DR. SL wrote the first draft of the manuscript with input from LD, DR and AG. All authors contributed to and have approved the final manuscript.

Conflict of interest

LD received an untied educational grant from Reckitt–Benckiser to monitor the extent of injection of buprenorphine-naloxone in Australia and to compare this with the injection of other forms of OST. All other authors declare no conflicts of interest.

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