Drug and Alcohol Dependence 115 (2011) 190–195

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

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

Rates and correlates of mortality amongst heroin users: Findings from the Australian Treatment Outcome Study (ATOS), 2001–2009

Shane Darke*, Katherine L. Mills, Joanne Ross, Maree Teesson

National Drug and Alcohol Research Centre, University of New South Wales, Sydney, NSW 2052, Australia

ARTICLE INFO

Article history:
Received 4 August 2010
Received in revised form
20 September 2010
Accepted 12 October 2010
Available online 3 December 2010

Keywords:
Heroin
Mortality
Overdose
Longitudinal
ATOS

ABSTRACT

The study aimed to determine mortality rates, standardised mortality ratios (SMRs), and correlates of mortality amongst the Australian Treatment Outcome Study (ATOS) cohort of 615 heroin users over the period 2001–2009. The cohort was followed for a total of 4820.1 person years. A total of 31 deaths (5% of the cohort) occurred across follow-up. The mean age at death was 34.5 years, and 58% were male. The most common cause of death was overdose (68%). The crude mortality rate was 6.43 per 1000 person years, with no gender difference, and the SMR was 4.56 (males = 2.95, females = 18.57). The only significant bivariate (hazard ratio = 3.69) and multivariate (adjusted hazard ratio = 3.03) correlate of mortality was a history of opioid overdose prior to baseline. Mortality rates were lower than those seen outside Australasia. Screening for overdose by those treating heroin users would be appropriate, and may contribute to reductions in overall mortality.

1. Introduction

Globally, opioids make the largest contribution to illicit drug-related death, carry a higher mortality risk than other commonly used drugs, and are associated with annual mortality rates typically ranging between one and three percent (Bartu et al., 2004; Darke et al., 2007a; Miller et al., 2007; Bauer et al., 2008; Bird, 2010; Stenbacka et al., 2010). It is worth noting that mortality rates vary considerably by geographic region. Rates appear highest in Asia, being approximately twice those of western Europe, three times those of North America and five times those of Australasia (Zhang et al., 2005; Bargagli et al., 2006; Miller et al., 2007; Quan et al., 2007; Azim et al., 2008; Vlahov et al., 2008; Degenhardt et al., 2009; Bird, 2010). This may reflect differences in underlying regional population mortality rates, as well as differences in access to drug treatment and health care.

The major causes of death are overdose, disease (predominantly AIDS), suicide and trauma (Bartu et al., 2004; Antolini et al., 2006; Soyka et al., 2006; Bargagli et al., 2006; Darke et al., 2007a; Degenhardt et al., 2009). The relative contribution of these, however, varies considerably across countries. In countries with a high HIV seroprevalence amongst injecting drug users (IDU), AIDS is a major cause of death, while in low prevalence countries overdose, suicide and trauma play far greater roles (Oppenheimer et al., 1994; Antolini et al., 2006; Bargagli et al., 2006; Bauer et al., 2008; Soyka et al., 2006; Vlahov et al., 2008; Degenhardt et al., 2009). A number of predictors of mortality have been identified. These include not being enrolled in drug treatment, injecting as a route of administration, HIV positive serostatus, older age, a longer heroin using career, polydrug use, the presence of clinically significant psychopathology and a suicide history (Quaglio et al., 2001; Bartu et al., 2004; Brugal et al., 2005; Soyka et al., 2006; Darke et al., 2007a; Azim et al., 2008; Bauer et al., 2008; Clausen et al., 2008; Stoove et al., 2009). Baseline predictors are of potentially great clinical importance for determining the mortality risk of patients at treatment in-take, which may affect treatment delivery.

The current study aimed to examine mortality rates, and correlates, amongst the Australian Treatment Outcome Study (ATOS) cohort over the period from commencement in February 2001 until October 2009. The cohort consists of entrants to treatment for heroin dependence in opioid maintenance, detoxification, and residential rehabilitation, as well as a comparison group of non-treatment users. The Australian setting for the cohort has a HIV seroprevalence amongst IDU of less than two percent, with population wide access to free health care (Mathers et al., 2008). At baseline, a wide range of drug use, overdose, psychological, health and psychosocial measures were collected (Ross et al., 2005). These data were used to determine what were the clinically important baseline characteristics predict death over the study period, as in similar other studies of opioid users (Gossop et al., 2002).

* Corresponding author. Tel.: +61 02 9385 0234; fax: +61 02 9385 0222.
E-mail address: s.darke@unsw.edu.au (S. Darke).

0376-8716/$ – see front matter © 2010 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.drugalcdep.2010.10.021

Specifically, the study aimed to:

1. Determine the mortality rates of the ATOS cohort.
2. Determine standardised mortality ratios (SMRs) for the cohort, stratified by gender.
3. Determine bivariate and multivariate associations of baseline characteristics with mortality rates.

2. Methods

2.1. Procedure

The data were collected as part of ATOS. Baseline interviews were conducted between February 2001 and August 2002, with three month (89% followed up), 12 month (80%), 24 month (76%) and 36 month (70%) follow-up interviews conducted. Prior to recruitment, all treatment agencies in the three modalities across the greater Sydney region were mapped. Agencies were then randomly selected, stratified by modality and area health service. The agencies comprised ten methadone/buprenorphine maintenance (MT) agencies, four drug free residential rehabilitation agencies (RR) and nine detoxification facilities (DTX). In addition, a group of heroin users not currently in treatment (NT) were recruited from needle and syringe programs in the regional health areas from which treatment entrants were recruited. Ethics approvals were obtained from the University of New South Wales, and all relevant area health services. Eligibility criteria were: (i) no treatment for heroin dependence in the preceding month, (ii) no imprisonment in the preceding month, (iii) agreed to give contact details for follow-up interviews, (iv) aged 18 years or over, and (v) fluent in English. The total baseline cohort was 615 heroin users: MT ($n = 201$), DTX ($n = 201$), RR ($n = 133$) and NT ($n = 80$). Participants were interviewed at baseline, and at 3, 12, 24 and 36 months post-baseline, and paid A$20 for completion of each interview. A search of the Australian National Death Index was conducted in October 2009, and details of deaths that had occurred amongst participants since 2001 was obtained. Participants were matched by full name, gender and date of birth.

2.2. Structured interview

At baseline, participants were administered a structured interview that included demographics, treatment history, drug use history, overdose history, suicide history and a range of psychopathology. Drug use, needle sharing, injection-related health problems and criminal behaviours over the month preceding interview were measured using the Opiate Treatment Index (OTI) (Darke et al., 1992). Current (1 month) global mental and physical health were measured using the Short-Form 12 (SF12), in which lower scores indicate poorer health (mean = 50, standard deviation = 10) (Ware et al., 1996). DSM IV diagnoses of current (1 month) Major depression and lifetime Post Traumatic Stress Disorder (PTSD) were obtained using the Composite International Diagnostic Interview (CIDI) (World Health Organization, 1993). Diagnoses of Antisocial Personality Disorder (ASPD) were obtained from the Diagnostic Interview Schedule (Robins et al., 1981), modified to obtain DSM IV diagnoses. International Classification of Diseases (10th edition) (ICD-10) diagnoses of BPD were obtained using the International Personality Disorders Examination Questionnaire used in the National Survey of Mental of Health and Wellbeing (Andrews et al., 1999).

2.3. Statistical analyses

Means and standard deviations were reported for continuous variables. Person years of follow-up were calculated from baseline interview date until date of death or censorship at October 2010, when the search was conducted. Crude mortality rates per 1000 person years (PY) with 95% confidence intervals (CI) were calculated, as were standardised mortality ratios (SMRs) by reference to age specific death rates in the Australian population (Australian Bureau of Statistics, 2010). Bivariate Cox proportional hazards regressions were performed to determine unadjusted hazard ratios (HR) for baseline characteristics in the domains of demographics, drug use, overdose, suicide, psychopathology health and crime. In order to determine independent predictors of mortality, a multivariate Cox proportional hazards regression was conducted. Age, sex and all variables with a p value <0.1 from the bivariate analyses were entered into the model. All analyses were conducted using PASW, Release 18 (SPSS Inc., 2009).

3. Results

3.1. Cohort characteristics at baseline

The mean age of participants was 29.3 years (SD 7.8, range 18–56), and 66% were male. The sample had completed a mean of 10.0 years of secondary education (SD 1.7, range 2–12), 29% had completed a trade/technical course, and six percent a university degree. The main sources of income were: social security allowances (46%), criminal activity (24%) and wage/salary (18%). It should be noted that these are main, and not sole, sources of income.

The mean age of first intoxication was 13.7 years (SD 3.3, range 2–34 years). The mean age of first heroin use was 19.6 years (SD 5.3, range 9–43 years), and the mean length of heroin use career at time of interview was 9.5 years (SD 7.4, range <1–35 years). The sample had used heroin on a mean of 20.1 days (SD 8.1, range 1–28) in the four weeks preceding interview, 54% reported a history of heroin overdose, and 8% were non-injectors. The sample had used a mean of 9.0 (SD 1.7, range 3–11) drug classes in their lives, and 4.8 (SD 1.7, range 2–9) in the preceding month. Ninety percent had previously been enrolled in a treatment program for opiate dependence. The mean SF12 global physical health score was 43.9 (SD 9.8, range 15.5–65.4) and the mean global health score was 31.7 (SD 11.1, range 8.9–67.3). A diagnosis of current (1 month) major depression was received by 25%, and 33% has attempted suicide. Forty one percent met criteria for a lifetime diagnosis of PTSD, 46% for a diagnosis of BPD and 73% for ASPD.

Across the 36 month follow-up period of ATOS, there was substantial cross-over between treatment modalities (Teesson et al., 2008). Amongst the NT group, 93% received some form of treatment by 36 months (MT 40%, RR 21%, DTX 50%). Similarly, there was substantial crossover between baseline treatment groups: MT (RR 5% and DTX 11%), RR (MT 26% and DTX 36%) and DTX (MT 33% and RR 37%).

3.2. Mortality

The cohort was followed for a total of 4820.1 PY. A total of 31 deaths (5%) occurred across follow-up, of which 18 (58%) were male. The crude mortality ratio was 6.43 per 1000 PY (95% CI 4.37–9.13 per 1000 PY), with no significant gender difference (Table 1). The SMR for the cohort was 4.56 (CI 3.09–6.47). Males had a SMR of 2.95 (CI 1.75–4.66) and females 18.57 (CI 9.89–31.52). Causes of death were: overdose ($n = 19$, 68%), disease ($n = 7$, 23%) and suicide ($n = 2$, 7%). In 3 cases the cause of death was unknown, due to lags in the National Death Index in providing full details of a death. Of the 19 known overdose fatalities, 16 had a history of overdose prior to enrolment in ATOS, and both suicides had made attempts prior to ATOS enrolment.

Table 1
Unadjusted and adjusted hazard ratio for all cause mortality amongst 615 heroin users.

Characteristics	No.	No. deaths	Person years	Mortality rate (per 1000 PY)	Multivariate statistics	
					Unadjusted hazard ratio	Adjusted hazard ratio
Total	615	31	4820.1	6.43(CI 4.37–9.13)	–	–
Demographics						
Age (Years)						
≥30	229	16	1767.3	9.05(CI 5.18–14.70)	1.84 (CI 0.82–4.10)	1.79 (CI 0.87–3.68)
<30	386	15	3052.8	4.91(CI 2.75–8.10)		
Sex						
Male	407	18	3195.4	5.63(CI 3.34–8.90)	0.70(CI 0.35–1.44)	0.76(CI 0.35–1.62)
Female	208	13	1624.6	8.00(CI 4.26–13.68)	1.00	
Previous treatment						
Yes	545	28	4278.7	6.54(CI 4.35–9.46)	1.17(CI 0.36–3.85)	–
No	69	3	541.4	5.54(CI 1.14–16.20)	1.00	
Entering treatment						
Yes	535	27	4196.3	6.43(CI 4.24–9.36)	1.00(CI 0.35–2.88)	–
No	80	4	623.8	6.41(CI 1.77–16.42)	1.00	
Modalities						
Maintenance	201	7	1596.8	4.38(CI 1.76–9.03)	0.67(CI 0.20–2.30)	–
Detoxification	201	10	1578.4	6.34(CI 3.04–11.65)	0.98(CI 0.31–3.11)	–
Residential rehabilitation	131	10	1021.0	9.79(CI 4.70–18.01)	1.53(CI 0.48–4.86)	–
Non-Treatment	80	4	623.8	6.41(CI 1.75–16.42)	1.00	
Drug use						
Length of career (Years)						
>5	382	23	2966.4	7.75(CI 4.92–11.63)	1.84(CI 0.82–4.10)	–
≤5	233	8	1853.7	4.32(CI 1.86–8.50)	1.00	
Heroin injector						
Yes	567	29	4435.7	6.54(CI 4.38–9.39)	1.25(CI 0.30–5.25)	–
No	48	2	384.3	5.20(CI 0.63–18.80)	1.00	
Heroin use (1 month)						
Daily	489	24	3834.2	6.26(CI 4.01–9.31)	0.88(CI 0.38–2.03)	–
Less than daily	126	7	985.8	7.10(CI 2.85–14.63)	1.00	
Alcohol (1 month)						
Yes	327	17	2552.4	6.66(CI 3.88–10.66)	1.08(CI 0.53–2.20)	–
No	288	14	2267.7	6.17(CI 3.38–10.36)	1.00	
Benzodiazepines(1 month)						
Yes	294	20	2287.0	8.75(CI 5.34–13.51)	2.00(CI 0.96–4.18)	1.59(CI 0.75–3.53)
No	321	11	2533.0	4.34(CI 2.17–7.77)	1.00	
Antidepressants (1 month)						
Yes	87	8	678.8	11.79(CI 5.09–23.22)	2.07(CI 0.93–4.63)	
No	528	23	4141.3	5.55(CI 3.52–8.33)	1.00	
Overdosed (Ever)						
Yes	334	25	2573.4	9.71(CI 6.29–14.34)	3.69(CI 1.51–9.90)[a]	3.03(CI 1.22–7.52)[a]
No	281	6	2246.7	2.67(CI 0.98–5.81)	1.00	
Suicide attempt (Ever)						
Yes	205	15	1596.5	9.40(CI 5.26–15.50)	1.90(CI 0.94–3.84)	1.40(CI 0.66–2.96)
No	410	16	3223.5	4.96(CI 2.84–8.06)	1.00	
Psychopathology						
Severe disability (SF12)						
Yes	303	18	2370.7	7.59(CI 4.50–12.01)	1.42(CI 0.70–2.90)	–
No	312	13	2449.4	5.31(2.83–7.42)	1.00	
Major depression						
Yes	151	11	1170.6	9.40(CI 4.69–16.81)	1.74(CI 0.83–3.62)	–
No	464	20	3649.5	5.48(CI 3.35–8.46)	1.00	
PTSD						
Yes	253	16	1977.5	8.09(4.62–13.14)	1.54(CI 0.76–3.11)	–
No	362	15	2842.5	5.28(2.95–8.70)	1.00	
ASPD						
Yes	440	20	3460.7	5.78(CI 3.53–8.93)	0.71(CI 0.34–1.48)	
No	175	11	1359.3	8.09(CI 4.04–14.48)	1.00	–
BPD						
Yes	280	17	2168.4	7.84(CI 4.57–12.55)	1.51(CI 0.74–3.06)	
No	335	14	2651.7	5.28(CI 2.89–8.86)	1.00	–
Health						
Severe disability(SF12)						
Yes	53	2	415.8	4.81(CI 0.58–17.38)	0.75(CI 0.18–3.14)	–
No	562	29	4404.3	6.58(CI 4.41–9.56)	1.00	
Crime (1 month)						
Yes	336	18	2635.9	6.83(CI 4.05–9.28)	1.14(CI 0.56–3.32)	–
No	279	13	2184.2	5.95(CI 3.17–10.18)	1.00	

[a] Significant association.

The mean age at death was 34.5 years (SD 8.1, range 20–55 years), with no difference between males and females (36.2 v 33.0, $p = 0.28$). The mean elapsed time between baseline and death was 4.4 years (SD 2.4, range 0.2–8.0 years), and mean length of heroin use 15.2 years (SD 8.6, range 1–32 years). There were no differences between the index treatment groups in the proportions of decedents ($p = 0.44$): MT (3.5%), RR (7.5%), DTX (5.0%) and NT (5.0%).

3.3. Predictors of mortality

The only significant bivariate association with mortality was a history of opioid overdose (Table 1). There was no significant difference in mortality rates for those who had overdosed on a single occasion (11.43 95% CI 5.24–21.72 per 1000 PY) and those who had overdosed on multiple occasions (8.96, 95% CI 5.12–14.54 per 1000 PY) There were no significant associations with demographic characteristics, length of drug use career, past month heroin and other drug use, suicide history, psychopathology, baseline health (one month) or baseline criminal activity (one month).

In order to determine independent predictors of mortality and adjusted hazard ratios, a multivariate Cox proportional hazards regression was conducted. Age (years), sex (Male = 1, Female = 0) and all variables with a p value <0.1 from the bivariate analyses were entered into the model: baseline benzodiazepine use (Yes = 1, No = 0), baseline antidepressant use (Yes = 1, No = 0), overdose history (Yes = 1, No = 0), baseline suicide attempt history (Yes = 1, No = 0). Again, the only significant predictor of mortality was a history of overdose prior to baseline (Table 1).

4. Discussion

Several major findings emerged. First, the cohort died at four and a half times the expected population rate, and at rates consistent with earlier Australian studies. Second, overdose was overwhelmingly the major cause of death. Finally, and related to this, overdose history was the *only* significant predictor of mortality.

The crude mortality rate of the cohort was consistent with earlier Australian studies of opioid users (Bartu et al., 2004; Digusto et al., 2004; Tait et al., 2008; Degenhardt et al., 2009), and was substantially lower than those seen in Europe, Asia and North America (Zhang et al., 2005; Bargagli et al., 2006; Miller et al., 2007; Quan et al., 2007; Vlahov et al., 2008; Bird 2010). In all probability this reflects the very low rates of HIV infection amongst Australian opioid users. In all Australian mortality studies conducted to date, disease has played a negligible role in mortality compared to cohorts from other regions. As noted above, it may also partially reflect the relative ease of access to free drug treatment in the Australian health system.

The demographic characteristics of decedents were typical of opioid deaths worldwide, in that they were predominantly male, aged on average in their thirties, injectors and had long heroin use careers. Despite the predominance of male fatalities, there was no gender difference in mortality rates, which is consistent with the bulk of studies internationally that report small, or no, gender differences (Oppenheimer et al., 1994; Sanchez-Carbonell and Seus, 2000; Bartu et al., 2004; Darke et al., 2007a; Bargagli et al., 2006; Bauer et al., 2008; Stenbacka et al., 2010). Consistent with earlier work, however, female SMRs were substantially higher than those of males, reflecting the lower base population mortality rate of females. If the mortality rates of male and female illicit drug users are similar, as here, the SMR of female drug users will always be far greater compared to other females, than for male drug users compared to other males.

Consistent with earlier Australian research, and the status of Australian IDU as a low HIV seroprevalence population, overdose dominated the cause of death (Bartu et al., 2004; Digusto et al., 2004; Tait et al., 2008; Degenhardt et al., 2009). In the Australian setting it is the risk of overdose that poses the single greatest threat to the life of the active heroin user. Interestingly, there was no discernable difference between single or multiple overdose histories prior to baseline. It is an overdose history *per se* that is of clinical relevance for mortality risk. The fact that an overdose history predicted subsequent mortality is consistent with earlier studies of non-fatal overdose in which a prior history of overdose strongly predicted future non-fatal overdose (Cook et al., 1998; Powis et al., 1999; Coffin et al., 2007; Darke et al., 2007c). Amongst the ATOS cohort over the initial 36 months, an overdose in any one year was associated with an approximately six fold increase in the risk of an overdose in the subsequent year (Darke et al., 2007c). The current study indicates that this risk extends to predicting death. Indeed, of the 19 known overdose deaths, 16 had overdosed prior to ATOS enrolment. The data are consistent with retrospective data of those previously attended for overdose, where overdose was associated with subsequent risk of overdose mortality (Stoove et al., 2009). Similarly, both known suicides had histories of suicide attempts, consistent with the cohort's pattern of past attempts strongly predicting future ones (Darke et al., 2007b).

The study is also of interest for what did *not* predict mortality. The most salient example was the absence of difference between those entering the treatment modalities and those not seeking treatment. As discussed earlier, treatment is associated with reduced drug use and mortality (Soyka et al., 2006; Clausen et al., 2008; Degenhardt et al., 2009). The natural history of the cohort, however, eroded the validity of such comparisons. By 12 months, three quarters of the NT group had entered drug treatment, and over 90% had done so by 36 months (Ross et al., 2006; Teesson et al., 2008). Similarly, there was substantial movement *between* the treatment modalities across time, which confounds any comparative analyses of mortality rates between modalities. Route of administration also did not predict mortality, despite being associated with lower rates of non-fatal overdose in the cohort (Darke et al., 2008), and being associated with lower death rates in other studies (Bird, 2010). As with treatment, however, comparisons were eroded by the fact that transitions between routes occurred, primarily from non-injecting to injecting (Darke et al., 2008). No form of psychopathology predicted death, in all probability reflecting the role of overdose, rather than suicide, as the predominant cause of death. The absence of health as a predictor reflects the low rate of HIV amongst Australian opioid users, and the relative health of the cohort. While the global health of the cohort was half a standard deviation below the population norm at baseline, by 12 months the cohort average had improved to population norms (Teesson et al., 2008).

The major implication of this research for treatment agencies concerns screening for overdose histories. Overdose was the major cause of death, and a history of overdose increased the risk of death three fold across follow-up. Indeed, it was *only* overdose histories that predicted death. Screening for overdose histories would appear prudent in determining patient risk, both for overdose and death, and tailoring intervention for high risk patients.

As in all studies, caveats must be borne in mind. First, caution should be exercised in extending conclusions to other heroin using populations. The ATOS cohort, like most cohorts, was regular heroin users, with an extensive previous treatment history. There may well be differences in mortality rates and correlates amongst less frequent heroin users. It must be borne in mind, however, that the overwhelming demographics of death amongst heroin users are long-term users, similar in characteristics to the ATOS cohort. Second, the exclusion of those who had been in prison in the month prior to baseline interview should be borne in mind, as this is a high risk period. Third, official statistics are always prone to lags

and possible omissions. We were thus not able to determine the cause of death for three cases. Finally, the detailed treatment and life events history of the cohort across the period were unknown, and follow-up interviews were restricted to 36 months. As noted above, however, this was a study of clinically relevant baseline characteristics that might be of use in determining the mortality risk for new treatment entrants. Also, the natural history of treatment means that any comparison between the modalities would be confounded by exposure to enrolments in multiple modalities.

In summary, death rates amongst this cohort were lower than those seen outside Australasia. Overdose dominated the deaths amongst the cohort, and an overdose history was the sole predictor of mortality. Screening for overdose by those treating heroin users would be appropriate, and may contribute to reductions in overall mortality.

Role of the funding source

This research was funded by the National Health and Medical Research Council, and the Australian Government Department of Health and Ageing. The funding source had no role in study design; in the collection, analysis or interpretation of data; in the writing of the report; or in any decision to submit the manuscript for publication.

Contributors

Professor Darke was involved in the design of the study, data analysis, and wrote the first draft of the manuscript. Dr Mills was involved in data collection, statistical analysis and the writing of the report. Dr Ross was involved in the design of the study, study co-ordination and the writing of the report. Professor Teesson was involved in the design of the study, project coordination, and the writing of the report.

Conflict of interest

There are no conflicts of interest to declare for any author.

Acknowledgments

This research was funded by the National Health and Medical Research Council, and the Australian Government Department of Health and Ageing.

References

Andrews, G., Hall, W., Teesson, M., Henderson, S., 1999. The Mental Health of Australians: National Survey of Mental Health and Wellbeing. Commonwealth Department of Health and Aged Care, Canberra.

Antolini, G., Pirani, M., Morandi, G., Sorio, C., 2006. Gender difference and mortality in a cohort of heroin users in the provinces of Modena and Ferrara, 1975–1999. Epidemiol. Prev. 30, 91–99.

Australian Bureau of Statistics, 2008. Deaths in Australia, 2008. Australian Bureau of Statistics, Canberra.

Azim, T., Chowdhury, E.I., Reza, M., Faruque, M.O., Ahmed, G., Khan, R., Rahman, M., Pervez, M.M., Jana, S., Strathdee, S.A., 2008. Prevalence of infections, HIV risk behaviours and factors associated with HIV infection among male injecting drug users attending a needle/syringe exchange program in Dhaka, Bangladesh. Subst. Use Misuse 43, 2124–2144.

Bargagli, A.M., Hickman, M., Davoli, M., Perucci, C.A., Schifano, P., Buster, M., Brugal, T., Vicente, J., for the Cosmo Working Group, 2006. Drug-related mortality and its impact on adult mortality in eight European countries. Eur. J. Public Health 16, 198–202.

Bartu, A., Freeman, N.C., Gawthorne, G.S., Codde, J.P., Holman, D.J., 2004. Mortality in a cohort of opiate and amphetamine users in Perth, Western, Australia. Addiction 99, 60–63.

Bauer, S.M., Loiple, R., Jagsch, R., Gruber, D., Risser, D., Tahu, K., Fischer, G., 2008. Mortality in opioid-maintained patients after release from an addiction clinic. Eur. Addict. Res. 14, 82–91.

Bird, S.M., 2010. Over 1200 drugs-related deaths and 190,000 opiate-users-years of follow-up: relative risks by sex and age group. Addict. Res. Theory 18, 194–207.

Brugal, M.T., Domingo-Salvany, A., Puig, R., Barrio, G., Garcia de Olalla, P., de la Fuente, L., 2005. Evaluating the impact of methadone maintenance programmes on mortality due to overdose and AIDS in a cohort of heroin users in Spain. Addiction 100, 981–989.

Clausen, T., Anchersen, K., Waal, H., 2008. Mortality prior to, during, and after opioid maintenance treatment (OMT): a national prospective cross-registry study. Drug Alcohol Depend. 94, 151–157.

Coffin, P.O., Tracy, M., Bucciarelli, A., Ompad, D., Vlahov, D., Galea, S., 2007. Indentifying injecting drug users at risk of nonfatal overdose. Acad. Emerg. Med. 14, 616–623.

Cook, S., Moeschler, O., Michaud, K., Yersin, B., 1998. Acute opiate overdose: characteristics of 190 consecutive cases. Addiction 93, 1559–1569.

Darke, S., Degenhardt, L., Mattick, R., 2007a. Mortality Amongst Illicit Drug Users: Epidemiology, Causes and Intervention. Cambridge University Press, Cambridge.

Darke, S., Hall, W., Heather, N., Wodak, A., Ward, J., 1992. Development and validation of a multi-dimensional instrument for assessing outcome of treatment among opioid users: the Opiate Treatment Index. Br. J. Addict. 87, 593–602.

Darke, S., Ross, J., Mills, K.L., Williamson, A., Havard, A., Teesson, M., 2008. Injecting and non-injecting heroin administration: transitions and treatment outcomes across 36 months. J. Drug Issues 38, 543–558.

Darke, S., Ross, J., Williamson, A., Mills, K.L., Havard, A., Teesson, M., 2007b. Patterns and correlates of attempted suicide by heroin users over a three year period. Findings from the Australian Treatment Outcome Study. Drug Alcohol Depend. 87, 146–152.

Darke, S., Ross, J., Williamson, A., Mills, K.L., Havard, A., Teesson, M., 2007c. Patterns of non-fatal heroin overdose over a three year period. Findings from the Australian Treatment Outcome Study. J. Urban Health 84, 283–291.

Degenhardt, L., Randall, D., Hall, W., Law, M., Butler, T., Burns, L., 2009. Mortality among clients of a state-wide opioid pharmacotherapy program over 20 years, risk factors and lives saved. Drug Alcohol Depend. 105, 9–15.

Digusto, E., Shakeshaft, A., Ritter, A., O'Brien, S., Mattick, R.P., NEPOD Study Group, 2004. Serious adverse events in the Australian National Evaluation of Pharmacotherapies for Opioid Dependence (NEPOD). Addiction 99, 450–460.

Gossop, M., Steward, D., Treacy, S., Marsden, J., 2002. A prospective study of mortality among drug misusers during a four year period after seeking treatment. Addiction 97, 39–47.

Mathers, B., Degenhardt, L., Phillips, B., Wiessing, L., Hickman, M., Strathdee, S., Wodak, A., Panda, S., Tyndall, M., Toufik, A., Mattick, R., for the 2007 Reference Group to the UN on HIV, Injecting Drug Use, 2008. Global epidemiology of injecting drug use and HIV among people who inject drugs, a systematic review. Lancet 372, 1733–1745.

Miller, C.L., Kerr, T., Strathdee, S.A., Li, K., Wood, E., 2007. Factors associated with premature mortality among young injection drug users in Vancouver. Harm Reduct. J. 4, doi:10.1186/1447-7517-4-1.

Oppenheimer, E., Tobutt, C., Taylor, C., Andrew, T., 1994. Death and survival in a cohort of heroin addicts from London clinics, a 22 year follow-up. Addiction 89, 1299–1308.

Powis, B., Strang, J., Griffiths, P., Taylor, C., Williamson, S., Fountain, J., Gossop, M., 1999. Self-reported overdose among injecting drug users in London, extent and nature of the problem. Addiction 94, 471–478.

Quaglio, G., Talamini, G., Lechi, A., Venturini, L., Lugoboni, F., Gruppo Intersert Di Collaborazione Scientifica, Mezzelani, P., 2001. Study of heroin-related deaths in north-eastern Italy 1985–98 to establish main causes of death. Addiction 96, 127–1137.

Quan, V., Vongchak, T., Jittiwutikan, J., Kawichai, S., Srirak, N., Wiboonnatakul, K., Razak, M.K., Suriyanon, V., Celentano, D.D., 2007. Predictors of mortality among injecting and non-injecting HIV-negative drug users in northern Thailand. Addiction 102, 441–446.

Robins, L.N., Helzer, J.E., Croughan, J., Ratcliff, K.S., 1981. National Institute of Mental Health Diagnostic Interview Schedule. Its history, characteristics, and validity. Arch. Gen. Psychiatry 38, 381–389.

Ross, J., Teesson, M., Darke, S., Lynskey, M., Ali, R., Ritter, A., Cooke, R., 2006. Short-term outcomes for the treatment of heroin dependence, findings from the Australian Treatment Outcome Study (ATOS). Addict. Disord. Their Treat. 5, 133–144.

Ross, J., Teesson, M., Darke, S., Lynskey, M., Ali, R., Ritter, A., Cooke, R., 2005. The characteristics of heroin users entering treatment, findings from the Australian Treatment Outcome Study (ATOS). Drug Alcohol Rev. 24, 411–418.

Sanchez-Carbonell, X., Seus, L., 2000. Ten-year survival analysis of a cohort of heroin addicts in Catalonia, the EMETYST project. Addiction 95, 941–948.

Soyka, M., Apelt, S., Lieb, M., Wittchen, H., 2006. One-year mortality rates of patients receiving methadone and buprenorphine maintenance therapy, A nationally representative cohort study in 2694 patients. J. Clin. Psychopharmacol. 26, 657–660.

SPSS inc., 2009. PASW Statistics, 18.0. SPSS inc., Chicago.

Stenbacka, M., Liefman, L., Romelsjo, A., 2010. Mortality and cause of death among 1705 illicit drug users, a 37 year follow-up. Drug Alcohol Rev. 29, 21–27.

Stoove, M.A., Dietze, P.M., Jolley, D., 2009. Overdose deaths following previous non-fatal heroin overdose, record linkage of ambulance attendance and death registry data. Drug Alcohol Rev. 28, 347–352.

Tait, R.J.N., Hanh, T.T., Hulse, G., 2008. Mortality in heroin users 3 years after naltrexone implant or methadone maintenance treatment. J. Subst. Abuse Treat. 35, 116–124.

Teesson, M., Mills, K.L., Ross, J., Darke, S., Williamson, A., Havard, A., 2008. The impact of treatment on 3 year outcomes for heroin dependence, findings from the Australian Treatment Outcome Study (ATOS). Addiction 103, 80–88.

Vlahov, D., Wang, C., Ompad, D., Fuller, C.M., Caceres, W., Ouellet, L., Kerndt, P., Des Jarlais, D.C., Garfein, R.S., 2008. Mortality risk among recent-onset injection drug users in five US cities. Subst. Use Misuse 43, 413– 428.

Ware, J.E., Kosinski, M., Keller, S.D., 1996. A 12-item Short-Form Health Survey, construction of scales, and preliminary tests of reliability and validity. Med. Care 34, 220–233.

World Health Organization, 1993. Composite International Diagnostic Interview (Version 1.1). World Health Organization, Vienna.

Zhang, L., Ruan, Y.H., Yang, Z.N., Liu, S.Z., Zhou, F., He, X.Y., Yin, L., Qin, G.M., Shao, Y.M., 2005. A 1-year prospective cohort study on mortality of injecting drug users. Chin. J. Epidemiol. 26, 190–193.