

Risk of fatal overdose during and after specialist drug treatment: the VEdeTTE study, a national multi-site prospective cohort study

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ABSTRACT

Background Specialist drug treatment is critical to overdose prevention; methadone maintenance is effective, but we lack evidence for other modalities. We evaluate the impact of a range of treatments for opiate dependence on overdose mortality. **Methods** Prospective cohort study of 10 454 heroin users entering treatment 1998–2001 in Italy followed-up for 10 208 person-years in treatment and 2914 person-years out of treatment. Standardized overall mortality ratios (SMR) estimate excess mortality risk for heroin users in and out of treatment compared to the general population. Cox models compare the hazard ratio (HR) of overdose between heroin users in treatment and out of treatment. **Results** There were 41 overdose deaths, 10 during treatment and 31 out of treatment, generating annual mortality rates of 0.1% and 1.1% and SMRs of 3.9 [95% confidence interval (CI) 2.8–5.4] and 21.4 (16.7–27.4), respectively. Retention in any treatment was protective against overdose mortality (HR 0.09 95% CI 0.04–0.19) compared to the risk of mortality out of treatment, independent of treatment type and potential confounders. The risk of a fatal overdose was 2.3% in the month immediately after treatment and 0.77% in the subsequent period; compared to the risk of overdose during treatment the HR was 26.6 (95% CI 11.6–61.1) in the month immediately following treatment and 7.3 (3.3–16.2) in the subsequent period. **Conclusions** We demonstrate that a range of treatments for heroin dependence reduces overdose mortality risk. However, the considerable excess mortality risk in the month following treatment indicates the need for greater health education of drug users and implementation of relapse and overdose death prevention programmes. Further investigation is needed to measure and weigh the potential benefits and harms of short-term therapies for opiate use.

Keywords Cohort study, heroin dependence, mortality, overdose, treatment.

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INTRODUCTION

Heroin users are at high risk of premature mortality [1,2], with annual mortality rates of between 1% and 3% [3], six to 30 times higher than a similarly aged general population, and contributing an estimated 10% of adult mortality (aged 15–54 years) in many European cities [3]. Overdose is the most common cause of death among heroin users and accounts for many preventable deaths among young adults [4]. The risk of death from overdose is substantially lower in individuals who enrol in metha-

done maintenance treatment (MMT) [5–7]. Patients who dropped out of methadone treatment were found to be more likely to die from overdose than patients who remained in treatment [8]. In contrast, one small study suggested that heroin users who complete residential/in-patient detoxification are more likely to overdose than those who fail to complete treatment [9]. In the United Kingdom, follow-up studies of prisoners and drug users leaving prison suggest that the risk of death, primarily through overdose, is elevated in the period immediately following release [10,11]. Loss of tolerance to the toxic

effects of heroin (among those who resume drug consumption after abstinence) is the most likely explanation for the excess mortality [12]. Further, although the results of several observational studies concerning the protective effect of methadone maintenance are consistent, debate on the effectiveness of MMT in reducing overdose mortality rates continues [13,14]. Very few studies have compared the effectiveness of different treatment types in preventing mortality from overdose, and only pharmacological treatments have been considered [15,16]. The Italian health-care system offers a unique opportunity to compare the effects of various treatments for drug addiction. Dependent heroin addicts receive a variety of treatment options at the local government-managed centre in their area of residence, provided directly at the centre or by private health-care services. The aim of the present paper is to evaluate the impact of each treatment offered by treatment centres in Italy on mortality from overdose; and to estimate and compare overdose mortality during treatment with periods after treatment.

METHODS

Study population

The VEdeTTE study recruited 10 454 heroin users at 115 (23%) public treatment centres (PTC) of 554 centres working within the National Health Service in Italy at the time of the study [17]. In each treatment centre we studied subjects over an 18-month period between September 1998 and March 2001. Clinical history and personal information were collected at the intake interview, and each treatment episode over the study period was recorded. We analysed 10 258 (98%) patients who had treatment information available. Patients could receive more than one type of treatment at the same time and have multiple periods of similar or different treatments. These included: (i) MMT; (ii) Therapeutic Community (residential or semi-residential); (iii) methadone detoxification; (iv) other pharmacological detoxification and treatment, including opiate antagonist, symptomatics and neuroleptic drugs; and (v) psychosocial treatments (including psychotherapy, counselling, social advice and job guidance). All treatments, except the residential Therapeutic Community and 0.6% of detoxification with drugs other than methadone, were offered in out-patient settings. The study had ethical approval by the Italian Data Protection Agency. All participants provided written informed consent.

Data analysis

Vital status was assessed first at the treatment centre; when the centre did not have track of the patient, we

searched the Registry Office of the last municipality of residence which keeps track of any residence change and vital status. Follow-up was complete for 96.3% of subjects; personal identifiers were used following the rules of privacy regulation.

Cause of death was coded according to the International Classification of Diseases (ICD) (IX revision). The following ICD codes were selected: 292; 304.0–.9; 305.2–.9; 965.0–.9; 969.0–.9; E850–E858; E980.0–.5–.9; E950.0–.5–.9; E962. According to the European Monitoring Centre for Drugs and Drug Addiction protocol for drug-related deaths [18], these codes correspond mainly to the causes of death 'drug dependence' and 'poisoning'. Person-years at risk were calculated from the start of treatment to the end of the 18-month study period in each centre or until the date of death.

In order to limit potential bias of misclassifying deceased patients as being out of treatment, we defined 'out of treatment' from the second day of absence of pharmacological treatment, or after the median time between scheduled appointments following absence from psychosocial treatment.

Standardized mortality ratios (SMR) were calculated based on death rates of the Italian population aged between 15 and 65 years (year 1998). Two-sided 95% confidence intervals (95% CI) for SMRs were based on the Poisson distribution.

We applied the extended Cox model with both time-dependent and fixed covariates to estimate the hazard ratio (HR) and corresponding 95% CI of mortality from overdose among heroin users 'out of treatment' versus those 'in treatment'. The mortality rate of heroin users in treatment was calculated by dividing the number of patients who 'died in treatment' by the total person-years in treatment, and similarly for the mortality rate out of treatment. In order to estimate the risk of overdose death according to treatment typology we considered person-time spent in each individual treatment as the denominator and deaths that occurred during a specific treatment as the numerator. We analysed the following types of treatment: methadone maintenance, Therapeutic Community living, methadone detoxification, psychosocial treatments and pharmacological treatments other than methadone. Psychosocial treatments, if in combination with methadone or Therapeutic Community, were coded under the latter. In order to take into account the potential effect of patient mix, besides the time-dependent variables type of treatment and age, we included in the multivariate analysis all the available information which might proxy severity of addiction, gender, cocaine use, human immunodeficiency virus (HIV) status, psychiatric diagnoses, route of administration, age at first heroin use, previous

Table 1 Hazard ratio of overdose mortality for heroin users in treatment, VEdeTTE study.

	Number of deaths (41)	Person-years	Rate 1000 py	Crude hazard ratio	Adjusted hazard ratio*	95% confidence intervals	
Out of treatment	31	2 913.79	10.64	1.00	1.00		
In treatment	10	10 207.72	0.98	0.09	0.09	0.04	0.19
In treatment							
Methadone maintenance	7	5 751.28	1.22	0.11	0.10	0.04	0.24
Therapeutic Community	0	1 188.94	–	–	–	–	–
Methadone detoxification	1	1 495.72	0.67	0.06	0.07	0.01	0.50
Other pharmacological	1	422.59	2.37	0.22	0.37	0.05	2.76
Psychosocial	1	1 349.23	0.74	0.07	0.07	0.01	0.55

*Adjusted for age, gender, psychiatric comorbidity, HIV status, previous non-fatal overdose, route of administration, length of use. py: Person-years.

Table 2 Hazard ratio of overdose mortality for heroin users out of treatment by treatment and by time since last treatment, VEdeTTE study.

	Number of deaths (41)	Person-years	Rate 1000 py	Crude hazard ratio	Adjusted hazard ratio*	95% confidence intervals	
In treatment	10	10 207.72	0.98	1	–	–	–
Out of treatment	31	2 913.79	10.64	10.86	11.11	5.29	23.35
Out of treatment							
Methadone maintenance	9	997.68	9.02	9.21	8.26	3.27	20.88
Therapeutic Community	5	231.74	21.58	22.02	23.00	7.63	69.31
Methadone detoxification	7	814.06	8.60	8.78	9.35	3.46	25.26
Other pharmacological	7	612.20	11.43	11.67	12.09	4.48	32.60
Psychosocial	3	250.46	11.98	12.23	22.31	5.88	84.58
Time since last treatment (days)							
≤ 30	13	561.44	23.15	23.64	26.57	11.56	61.10
> 30	18	2 352.36	7.65	7.81	7.29	3.28	16.22

*Adjusted for age, gender, psychiatric comorbidity, HIV status, previous non-fatal overdose, route of administration, length of use. py: Person-years.

overdose, imprisonment, educational level, living situation and employment status as fixed variables.

RESULTS

The study population of 10 258 heroin users provided 13 538.2 person-years of observation, of whom 10 208 person-years were in treatment (78%) and 2914 (22%) out of treatment. More than 80% of the clients were male with an average age of 31.5 at recruitment; 60% were employed, 72% were injecting drug users (IDU), starting at an average age of 21%, 8% were HIV positive, 13% had psychiatric comorbidity and 41% reported non-fatal overdose history.

One hundred deaths for all causes occurred within the 18-month study period, 37 while in treatment and 63 out of treatment. The excess mortality risk for all causes (SMR) compared to the general population of the same age and gender was 3.9 (95% CI: 2.8–5.4) for heroin users in treatment and 21.4 (95% CI: 16.7–27.4) for those out of treatment.

Forty-one of the deaths were from overdose: 31 occurred out of treatment and 10 in treatment.

Table 1 shows that the overdose mortality rate was more than 11 times lower in treatment compared to 'out of treatment' (HR, 0.09, 95% CI 0.04–0.19). The protective effect during treatment persisted for several modalities, including methadone maintenance (HR 0.10, 95% CI 0.04–0.24); methadone detoxification (HR 0.07, 95% CI 0.01–0.50); and psychosocial treatments (HR 0.07, 95% CI 0.01–0.55). No overdose deaths were observed among the 1189 person-years in a Therapeutic Community. Person-years of exposure to other pharmacological treatments were comparatively small, and although the mortality rate was lower than for heroin users out of treatment, the HR was non-significant (HR 0.37, 95% CI 0.05–2.76).

Table 2 shows that the risk of death is substantially higher in the first 30 days following treatment at 2.3% than in the subsequent period 31 days or more after leaving treatment at 0.8%. The adjusted HR were 26.6 (95% CI 11.6–61.1) and 7.3 (95% CI 3.3–16.2) for the

first 30 days after treatment and 31 days or more, respectively, compared to heroin users in treatment. Heroin users in the 30 days since last treatment experience an adjusted HR of overdose death of 3.65 (95% CI: 1.74–7.62) compared to the overdose risk in the subsequent period 31 days or more since last treatment.

Treatment dropouts comprised nine of nine and four of five of the deaths in heroin addicts ceasing methadone maintenance and Therapeutic Communities, respectively. In contrast, six of seven patients who died after methadone detoxification had completed treatment. The risk ratio (RR) of mortality comparing 'completers' of methadone detoxification treatment with those who ceased methadone detoxification early ('dropouts') was RR = 4.14 (95% CI: 0.59–29.1).

DISCUSSION

The key findings of the study are that heroin users have a substantially reduced risk of death during a range of treatments, and that the risk of death following treatment is higher in the period immediately following treatment dropout or cessation. We corroborate and add to the literature showing that methadone substitution therapy is protective against overdose mortality [6,7,19], and provide evidence that the protective effect of treatment extends to methadone detoxification, Therapeutic Communities and psychosocial treatments, and may extend to other pharmacological therapies. We show that the risk of death among heroin users in treatment, although still raised compared to the general population, is substantially lower than heroin users out of treatment who have an SMR of more than 20. Finally, the study shows a higher excess risk of overdose in the first 30 days after treatment completion or cessation: more than three times higher than the subsequent period 31 or more days after treatment.

The comparative size of this excess in the period immediately following treatment suggests a further hypothesis: that any reduction in overdose risk during treatment may, under some circumstances, be outweighed by the increase in overdose risk immediately following treatment. In order to elaborate the hypothesis we computed the rate of overdose mortality in the first 30 days in any treatment combined with the rate of overdose mortality in the first period out of treatment, and compared it with the rate of overdose mortality of 2 consecutive months out of treatment. This simulation suggested that a too-short period of *any* treatment may result in excess mortality; however, the uncertainty was large and the power of the study was not sufficient to discriminate between different treatment modalities. Other studies are required to corroborate the size of the excess mortality risk following treatment cessation or dropout,

and to examine the implications and weigh the potential risks and benefits of short-term treatments.

Strengths and limitations

A key strength of the VEdeTTE study of Italian heroin users is the largest recent cohort of heroin addicts recruited from treatment sites to assess drug-related mortality and overdose [17].

We acknowledge a number of limitations to the study design or interpretation of the findings. First, a randomized controlled trial (RCT) would have provided the strongest evidence for treatment effectiveness, as potential confounders would be distributed equally between intervention and control groups. However, such a design would be impractical (and unethical) to implement [20] in order to assess impact of treatment on overdose mortality, partly because of the study size required but principally because it would be unacceptable to deny patients treatment. Instead, we adopted what may be considered the next best study design (cohort/longitudinal follow-up study) in the hierarchy of epidemiological evidence.

Secondly, patients were selected at point of drug treatment, and although representative of heroin users seen in clinical practice in Italy, they may not be representative of the total population of heroin users. In particular, this matters if the risk of overdose among our study participants out of treatment is different from the general overdose risk of *all* heroin users who are not in treatment, including those who have not yet presented. However, overdose mortality rates estimated in the overall out-of-treatment period in our study was similar to the one estimated in another study on injection drug users identified as out of treatment [21].

Thirdly, patient factors may have affected treatment assignment and, consequently, the case mix could have produced biased results. However, a previous analysis on the same cohort showed that higher-risk patients (such as injecting users, patients adopting risk behaviours and HIV infected) are more likely to enter methadone maintenance than methadone detoxification [22]. In the present analysis we adjusted for some key confounders that are related to overdose risk and may be associated with treatment, including addiction severity, socioeconomic status, age and sex, but there may be other confounders and some selection bias that we have not accounted for that would bias the results.

Fourthly, the number of years of follow-up of the participants out of treatment was substantially less than follow-up of participants during treatment. Therefore, the confidence intervals around the estimated mortality out of treatment were wider compared to heroin users in treatment; and the power of the study (at this stage)

to examine differences in overdose risk between treatment modalities was limited. However, the study still followed-up nearly 3000 person-years out of treatment, which compares very favourably with many other overdose mortality studies [23].

Fifthly, the SMR compared the mortality of the general population in Italy with our cohort of heroin users. In part, this will lead to an underestimate of the true SMR because heroin users have not been removed from the denominator, but also may overestimate the SMR because we have not adjusted for social position and other potential confounders that may increase mortality risk apart from heroin use.

Implications

The study has important implications and raises essential hypotheses for the impact of specialist drug treatment on fatal overdose in Italy and other countries in Europe and elsewhere. Of course, it is possible that our results are not generalizable to other countries, although the mix of provision and client characteristics are similar to many other European countries [24], so evidence against our findings would need to be generated from similar longitudinal studies.

We show that a range of specialist drug treatment therapies are protective during treatment which we may interpret as due to a reduction in heroin injecting. Most of the deaths in patients receiving methadone maintenance or living in long-term Therapeutic Communities were treatment dropouts, which we interpret as due to a greater risk of relapse into heroin injecting, thereby increasing the risk of a fatal overdose among dropouts compared to those remaining in treatment. Similar results were observed in another study on methadone maintenance [25]. Treatment retention should be a key priority for long-term and maintenance therapies as part of an overdose prevention programme [8,26,27]. In direct contrast, the mortality risk was higher among patients completing methadone detoxification services compared to those who ceased or dropped out which we interpret, as did Strang and colleagues [9], that greater reductions in opiate 'tolerance' were achieved by those completing treatment, putting them at greater risk of an overdose if they relapsed (compared to those who dropped out). An adequate post-treatment follow-up should be considered as an integral component of any treatment aimed at abstinence.

We provide strong evidence that the risk of overdose is elevated in the period immediately following treatment, no doubt in part because of a loss of tolerance to heroin increasing the risk of death if the patient relapses. We do not know, however, whether the elevated mortality risk is due entirely to a greater relapse rate in the month imme-

diately following treatment or whether there may also be other differences in the circumstances, characteristics or drug use of patients who relapse early after treatment, which puts them at a greater overdose risk than those who relapse at a later date.

CONCLUSIONS

Heroin users have a substantial risk of death, primarily from fatal overdose. We show that a range of specialist drug treatments are protective, but that special attention should be given to the period immediately following treatment. Drug treatment programmes need to educate their clients about the risks of post-treatment relapse and overdose, and overdose death prevention programmes need to be implemented that take account of the risks following treatment. Moreover, further studies are required that can measure and weigh the potential benefits and harms of short-term therapies for opiate use.

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