Opioid overdose risk during and after drug treatment for heroin dependence: An incidence density case–control study nested in the VEdeTTE cohort

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Abstract

Introduction and Aims. To corroborate protective effects of a range of drug treatment modalities against overdose mortality risk.
Design and Methods. Nested case–control study, with incidence density sampling, selecting controls retrospectively at each case event. Cases and controls came from a sub-cohort of opioid-dependent patients (n = 4444) from two Italian regions (Lazio and Piedmont). From 1998 to 2005, there were 91 overdose deaths (cases) matched to 352 controls. The primary outcome was overdose mortality and the primary exposure was drug treatment: opioid agonist treatment (OAT), opioid detoxification, residential community, psychosocial and other pharmacological treatment. Conditional logistic regression models generated intervention effects comparing mortality risk in and out of treatment, adjusting for confounding variables.
Results. Overall, drug treatment reduced overdose mortality risk by 80% [adjusted odds ratio (AOR) 0.18, 95% confidence interval (CI) 0.10–0.33, P < 0.001] compared to being out of treatment. There was a particularly strong protective effect of OAT on overdose mortality (AOR 0.08, 95% CI 0.03–0.23, P < 0.001) compared to being out of treatment. There was evidence of a substantially elevated risk of overdose in the first month of leaving treatment (AOR 23.50, 95% CI 7.84–70.19, P < 0.001) compared to being in treatment.
Discussion and Conclusions. The nested case–control design strengthened earlier findings that OAT in Italy has strong protective effects on overdose mortality risk, much stronger than has been previously seen in other Western European settings.

Introduction

In Western Europe, there is a substantially elevated risk of mortality for people who use illicit opioids compared to the general population [1]. Currently, overdose is the leading cause of death among this population and is increasingly prevalent [2–4]. Opioid agonist treatment (OAT) is an essential medicine for treating opioid dependence [5] and multiple studies have shown that the risk of overdose is substantially higher for people who are not engaged in OAT [6–10]. This risk has been found to be more pronounced in the month immediately following treatment (i.e. completing or leaving treatment) [6,7,11,12].

Previously, we investigated the protective effect of multiple treatment modalities on overdose mortality risk and found that 'retention in any treatment' was strongly protective, reducing overdose risk by 90% [hazard ratio 0.09, 95% confidence intervals (CI) 0.04–0.19] [7]. The previous study was a large prospective cohort (n = 10 258) with a comparatively short exposure period out of treatment (n = 2914 person-years) and relatively few overdose deaths (n = 41). Where data on exposures are not updated, and need to be collected, the nested case–control design is beneficial as it is a more efficient way of increasing power and can provide direct estimates of intervention effects [13].

In this study, we undertook a nested case–control design using incidence density sampling that would extend the follow-up period, decrease the sample size and more efficiently strengthen and test the findings previously reported from this cohort.

Methods

Participants

Details of the original cohort are described elsewhere [7]. Briefly, participants were recruited at 115 of 554 (23.0%) public treatment centres working within the National Health Service in Italy during 1998–1999 [14]. The original VEdeTTE cohort consisted of 10 454 people who use heroin. From this broader cohort, we had capacity to conduct a further study in two Italian regions (Piedmont and Lazio), which comprised 4444 participants. Among this sub-cohort, from September 1998 to 31 December 2005, 316 deaths occurred and 95 were due to overdose (Figure S1, Supporting Information).

Design

This study is a nested case–control design where the cases were those who had fatally overdosed over the follow-up period. Adopting an incidence density sampling procedure, four controls for each overdose death were randomly extracted from the cohort (coded as alive on the date of the case's death, i.e. the index date for controls). Participants were matched on region, age (i.e. the age of the case ±5 years) and sex. Participants could be matched with multiple cases and a case could potentially be a control of a case who had died before them. In total, 380 controls were extracted.

Of 95 cases, four were subsequently excluded due to missing treatment participation information (see participant flowchart in Figure S2). Out of 380 controls, 28 were excluded (16 controls paired with the excluded cases and 12 controls had missing treatment information). A total of 91 cases and 352 controls were included in the study.

Measures

The primary outcome was death due to overdose. Assessors who extracted data from clinical records were blind to whether subjects were a case or control. Vital status information was first retrieved from the clinical records retained from the participant's treatment centre, then (if unavailable) from the Registry Office of the last municipality of residence, which keeps track of any change in residence or vital status. Follow up was completed for 97.8% of subjects. Cause of death was coded according to the International Classification of Diseases (ninth revision), and overdose deaths were consistent with

the European Monitoring Centre for Drugs and Drug Addiction definition at the time of extraction and the previous study [7,15]. The codes corresponded mainly to the causes of death, 'drug dependence' and 'poisoning' (including accidental).
The primary exposure was drug treatment type. Information on any treatment administered in the last 2 months before the death for cases, and index date for controls, were collected from clinical records, including type of treatment, starting and closing date, dose, frequency and treatment status (incomplete or completed). There were 13 treatment types that were aggregated into five groups for analysis: OAT (methadone maintenance and buprenorphine maintenance treatments), opioid detoxification (methadone detoxification and buprenorphine detoxification), other pharmacological treatment (naltrexone maintenance, detoxification with non-opioid drugs and therapy with other psychotropic drugs), residential community (residential and semi-residential treatment facilities) and psychosocial (social advice and counselling). For those out of treatment in the last 2 months before the index date, information on treatments (type and date of last administration) in the month before discharge/last attendance was collected. Being considered 'out of treatment' differed between modalities:

- Pharmacological treatment: from the second day of absence.
- Residential community: from the second day after leaving treatment.
- Psychosocial treatment: from the day after the first missed visit.

Baseline demographic data assessed at enrolment in the VEDeTTE cohort included sex, age, educational level, marital status, employment and housing status. Drug use and risk behaviours included type and frequency of drug use, heroin administration method, age at first heroin use, history of overdose, health risk behaviours, mental and physical health status, voluntary access to drug treatment and criminality in the last 12 months [14].

Statistical analysis

The study aimed to assess mortality risk during and immediately after periods of drug treatment and test and replicate the findings from the previous paper [7]. The nested case–control study had 99% power to detect a difference in mortality risk of at least three times between in and out of treatment, assuming 30% exposure to drug treatment.
The effect of being in or out of treatment at the time of death for overdose was assessed using a conditional logistic regression model (as the case–controls were matched). The nested design and sampling of controls meant that the estimated odds ratios (OR) approximate risk ratios and can be directly compared to the results from the previous cohort [13]. The same model was applied to evaluate the effect of time since the disruption in treatment.
Potential confounders were identified using univariable logistic regression models. Variables associated with the outcome (P-value ≤ 0.2) were included in the multivariable models (homelessness, HIV positivity, alcohol use, legal problems and overdose reported at baseline). Missing information at baseline was negligible for any of the assessed characteristics.

Ethics

At enrolment into treatment, participants gave informed consent to participate in this study. Study protocol complied with the Italian law about confidentiality (D.Lgs 675/96 followed by D.Lgs 196/2003).

Results

We followed up 91 cases and 352 controls for an average of 6.8 years (from 1998 to 2005). Table 1 shows demographic information for cases, controls and the original VEdeTTE sub-cohort. Of those in treatment at the index date, 20 (8.8%) were cases and 207 (91.2%) were controls. Most participants were in OAT (52.9%), psychosocial treatment (18.9%), residential community (15.4%) or opioid

detoxification (11.9%). For those out of treatment, the most commonly recorded last treatment was psychosocial (30.1%), followed by OAT (26.8%) and opioid detoxification (24.1%).
Table 2 shows that, compared to those out of treatment, those in treatment showed a reduced risk of overdose mortality (OR 0.19, 95% CI 0.10–0.33, P < 0.001). This effect remained stable after controlling for potentially confounding variables [adjusted odds ratio (AOR) 0.18, 95% CI 0.10–0.33]. The effect sizes differed by treatment type with only OAT (AOR 0.08, 95% CI 0.03–0.23, P < 0.001) and residential community (AOR 0.22, 95% CI 0.06–0.76, P = 0.019) yielding strong protective effects. The unadjusted risk of death for overdose was 5.40 (95% CI 3.05–9.56, P < 0.001) for those out of treatment, and the adjusted risk of death was 5.46 (95% CI 3.02–9.88, P < 0.001). In the first 30 days after leaving treatment, the risk of overdose was substantially higher (OR 15.07, 95% CI 5.79–39.22, P < 0.001), and slightly strengthened after adjusting for potentially confounding variables (AOR 23.50, 95% CI 7.84–70.19, P < 0.001). The risk of acute mortality (excluding overdose) in and out of treatment, and in the first 30 days of leaving treatment, are provided in Tables S1 and S2.

Discussion

We corroborated earlier findings of the protective effect of drug treatment in Italy. Using a nested case–control design, we found that overdose mortality was more than 23 times higher in the first month out of treatment compared to in treatment for people who are heroin dependent. OAT had a very strong protective effect with a reduction in the risk of overdose mortality by over 90%.
This study strengthens and elaborates on previous findings that drug treatment, especially OAT, is particularly protective in Italy. The crude mortality rate estimated previously for the VEdeTTE cohort was 12.0 per 1000 person-years [16], lower than what was estimated for Western European cohorts previously [22.2 (95% CI 19.6–24.7) per 1000 person-years] [3]. Therefore, it may be that OAT in Italy is more effective in reducing overdose risk compared to other European settings.
There are several limitations that need to be considered. First, our treatment exposure refers only to whether the case or control was engaged in treatment for 2 months, so we could not test whether treatment duration contributed to mortality risk. It has been estimated that increasing the average treatment duration by 3 months could incur a 5% decrease in mortality [17]. Also, our treatment exposure refers to centres participating in the study and may misclassify other treatment types as being ‘out of treatment’ (e.g. private clinics). Nonetheless, the number of people who use heroin attending private clinics is estimated to be low in Italy [18], the treatment effect was considerable and misclassification would be more likely to lead to an under-estimate.
Compared to other settings, the quality of clinical records kept for OAT and therapeutic communities in Italy is of good quality. For therapeutic communities, there is a refund system that is based on treatment administration and days of attendance. Maintaining clinical records is not compulsory for the other types of treatment; therefore, the completeness of those clinical records could be variable. Due to the study design, however, any recording bias is likely to be nondifferential as it can affect both cases and controls.

Conclusion

We strengthened the assertion that drug treatment in Italy is protective of overdose mortality; it is necessary to educate people who use opioids about the risk of overdose, especially in the period that immediately follows treatment.

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Conflict of Interest

The authors have no conflicts of interest.

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Table 1. *Descriptive characteristics and comparisons of the cases and controls, the VEdeTTE sub-cohort and treatment engagement*

Characteristics at baseline	Cases, *n* (%) *n* = 91	Controls, *n* (%) *n* = 352	Cases vs. controls *P*-values	VEdeTTE cohort (*n* = 4444) *n* = 4444
Men	73 (80.2)	282 (80.1)	0.982	3671 (82.6)
Age, years			0.607	
<30	14 (15.4)	56 (15.9)		1745 (39.3)
30–34	18 (19.8)	92 (26.1)		1314 (29.6)
35–39	33 (36.3)	118 (33.5)		851 (19.2)
≥40	26 (28.6)	86 (24.4)		534 (12.0)
Marital status			0.227	
Never married	63 (69.2)	230 (65.3)		2900 (65.3)
Married	14 (15.4)	44 (12.5)		604 (13.6)
De facto	10 (11.0)	33 (9.4)		448 (10.1)
Separated/divorced	<5 (4.4)	40 (11.4)		435 (9.8)
Widowed	0 (0.0)	5 (1.4)		52 (1.2)
Education level[a]			0.092	
Compulsory education	69 (75.8)	260 (73.9)		3296 (74.2)
More than compulsory	22 (24.2)	89 (25.3)		1148 (25.8)
Homeless	8 (8.8)	7 (2.0)	0.005	98 (2.2)
Unemployed	41 (45.1)	129 (36.6)	0.276	1479 (33.3)
Voluntary drug treatment access	78 (85.7)	285 (81.0)	0.488	3701 (83.3)
Cocaine use	35 (38.5)	149 (42.3)	0.309	1718 (38.7)
Alcohol use	26 (21.3)	84 (17.9)	0.438	758 (17.1)
History of overdose	81 (66.4)	200 (42.6)	<0.001	1919 (43.2)
HIV+	29 (8.2)	9 (9.9)	0.616	429 (9.7)
Psychiatric comorbidities	10 (11.0)	21 (6.0)	0.094	294 (6.6)
Age at first heroin use, mean (SD)	19.3 (4.2)	19.7 (4.4)	0.406	19.7 (4.5)
Legal problems in the last 12 months	38 (41.8)	119 (33.8)	0.300	1324 (29.8)
Region				
Piemonte	67 (73.6)	264 (75.0)	0.788	2723 (61.3)
Lazio	24 (26.4)	88 (25.0)		1721 (38.7)

Treatment engagement	In treatment[b] *n* (%) *n* = 227	Out of treatment[c] *n* (%) *n* = 216
Cases	20 (8.8)	70 (32.4)
Controls	207 (91.2)	146 (67.6)
Maintenance	120 (52.9)	58 (26.8)
Methadone	108 (47.6)	51 (23.6)
Buprenorphine	12 (5.3)	7 (3.2)
Detoxification	27 (11.9)	52 (24.1)
Methadone	25 (11.0)	52 (24.1)
Buprenorphine	5 (0.9)	0 (0.0)
Residential community	35 (15.4)	29 (13.4)
Psychosocial[d]	43 (18.9)	65 (30.1)
Other pharmacological[e]	<5 (0.9)	12 (5.6)

[a]Three of the 347 participants said they did not go to school. [b]Among those in treatment at the index date. [c]The last treatment for those out of treatment at the index date. [d]Psychosocial alone: psychosocial combined with other treatments is included in the other lines. [e]Other pharmacological: detoxification with non-opioid analogue or therapy with other psychotropic drugs.

Table 2. *Odds ratio (OR) and 95% confidence intervals (CI) of overdose mortality for people with heroin dependence in and out of treatment* (n = *443)*

Overdose mortality	Deaths (*n* = 91)	Crude OR	95% CI	*P*-value	Adjusted OR[a]	95% CI	*P*-value
Out of treatment	71	1	—	—	1	—	<0.001
In treatment	20	0.19	0.10–0.33	<0.001	0.18	0.10–0.33	—
In treatment							
Maintenance	5	0.09	0.03–0.24	<0.001	0.08	0.03–0.23	<0.001
Detoxification	<5	0.33	0.10–1.13	0.038	0.38	0.10–1.38	0.142
Residential community	<5	0.20	0.06–0.69	0.008	0.22	0.06–0.76	0.017
Psychosocial	8	0.51	0.22–1.19	0.089	0.50	0.21–1.21	0.126
In treatment	20	1	—	—	1	—	—
Out of treatment	71	5.40	3.05–9.56	<0.001	5.46	3.02–9.88	<0.001
Time since last treatment							
≤30 days	15	15.07	5.79–39.22	<0.001	23.50	7.84–70.19	<0.001
>30 days	56	4.40	2.44–7.96	<0.001	4.53	2.45–8.38	<0.001

There were no overdose deaths reported for buprenorphine detoxification or other pharmacological treatment. [a]Adjusted for homelessness, HIV positivity, alcohol use, legal problems and overdose reported at baseline.