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Patterns of Nonfatal Heroin Overdose Over a 3-Year Period: Findings From the Australian Treatment Outcome Study

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ABSTRACT *To determine annual patterns and correlates of nonfatal heroin overdose across 3 years, data were analyzed on 387 heroin users recruited for the Australian Treatment Outcome Study (ATOS), interviewed at 12, 24, and 36 months. A heroin overdose across follow-up was reported by 18.6%, and naloxone had been administered to 11.9%. Annual rates of overdose declined between baseline and 12 months and then remained stable. Previous overdose experience was strongly related to subsequent overdose. Those with a history of overdose before ATOS were significantly more likely to overdose during the study period. In particular, there was a strong association between overdose experience in any 1 year and increased overdose risk in the subsequent year. This is the first study to examine long-term annual trends in nonfatal heroin overdose. While overdose rates declined after extensive treatment, substantial proportions continued to overdose in each year, and this was strongly associated with overdose history.*

KEYWORDS *Cohort, Heroin, Overdose, Treatment.*

INTRODUCTION

Opioids constitute the single largest contribution to all illicit drug-related deaths, with opioid overdose being the major cause of premature death among heroin users.[1] Fatal overdose, however, represents only a small proportion of overdose events, with the proportion of heroin overdoses that result in death estimated to be between 2 and 4%.[2] While much of the focus regarding overdose is on fatalities, nonfatal overdose is of clinical significance, as it is associated with a range of serious sequelae, including pulmonary edema, bronchopneumonia, rhabdomyolysis, peripheral neuropathy, renal failure, cognitive impairment, and traumatic injuries sustained during overdose.[3]

The scope for clinically significant harm from overdose is high, as exposure appears frequent. Studies internationally report lifetime overdose histories ranging between one to two-thirds of heroin users.[4–15] To date, however, only two published studies have examined overdose longitudinally, both of which examined short-term (12 months) follow-up.[9,15] These studies demonstrated declines in overdose over a 12-month period, reductions that were associated with drug treatment. Whether reduced overdose levels are maintained across longer periods, however, is unknown.

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Given the serious sequelae of overdose and the risk of death from each episode, this is of great clinical significance. No study to date has examined the long-term patterns of overdose among heroin users or the factors associated with overdose in the longer-term. This is of particular clinical interest in ascertaining the effect of overdoses upon subsequent overdoses. In an earlier study, we reported that those who overdosed in the 12 months before treatment enrollment were significantly more likely to overdose again in the next 12 months.[9] Whether this reflects long-term overdose patterns is unknown, but it is of clear potential clinical significance in determining those who are at most risk of overdose and death.

Given the paucity of longitudinal data on overdose patterns, the current study aimed to examine overdose patterns across a 3-year period. The study aimed to determine whether the substantial improvements seen in overdose rates reported at 12 months among this overwhelmingly treatment exposed cohort were maintained over 36 months. The second major aim of the study was to examine the relationship between an overdose in any 1 year and its occurrence in the subsequent year. To determine the direct effects of an overdose in an individual on overdose in the subsequent year, the current manuscript analyzed data from the 387 cohort members who were interviewed at all three annual follow-up points. This analytical strategy was employed to allow directly comparable annual overdose data across each year of follow-up.

METHODS

Procedure

The data were collected from the New South Wales component of the Australian Treatment Outcome Study (ATOS). Baseline interviews were conducted between February 2001 and August 2002. ATOS is a longitudinal study of entrants to treatment for heroin dependence, recruited from randomly selected treatment agencies delivering methadone/buprenorphine maintenance treatment (MT), drug-free residential rehabilitation (RR), or detoxification (DTX). Subjects were recruited from 19 agencies treating heroin dependence in the greater Sydney region, randomly selected from within treatment modality. In addition, a comparison group of heroin users not currently in treatment (NT) were recruited from needle and syringe programs. Participants were interviewed at baseline, 3, 12, 24, and 36 months. It should be noted that, at the time of writing, data on fatalities across 36 months were not available from the National Death Index. Eligibility criteria were: (1) no treatment for heroin dependence in the preceding month, (2) no imprisonment in the preceding month, (3) agreed to give contact details for follow-up interviews, (4) aged over 17 years, and (5) fluent in English. Ethics approvals were obtained from the University of New South Wales and all relevant area health services.

Follow-up rates for the study were: 3 months: 89%, 12 months: 80%, 24 months: 76%, 36 months: 70%. As noted, to analyze annual trends in overdose, data was analyzed from the 387 cohort members who had been interviewed at all three annual follow-up points (representing 90% of those followed-up at 36 months and 63% of the entire baseline cohort).

Structured Interviews

At baseline, participants were administered a structured interview that addressed demographics, treatment history, drug use, heroin overdose history, history of

administration of the opioid antagonist naloxone hydrochloride to reverse overdose, criminal behaviors, health, and psychopathology. As in previous studies,[6–9] overdose was defined as any of the following symptoms occurring in conjunction with heroin use: difficulty breathing, turning blue, collapsing, losing consciousness, and being unable to be roused. It was emphasized that overdose did *not* mean acute heroin intoxication without these signs and symptoms. Participants were also asked about administration of the opioid antagonist naloxone hydrochloride, the principal drug used to treat overdoses. Drug use over the month preceding interview was measured using the Opiate Treatment Index (OTI).[16] General mental and physical health were measured using the Short-Form 12 (SF12), in which lower scores indicate poorer health.[17] DSM-IV diagnoses of current Major Depression and ICD-10 diagnoses of Borderline Personality Disorder (BPD) were obtained using the Composite International Diagnostic Instrument (CIDI).[18] Diagnoses of Antisocial Personality Disorder (ASPD) were obtained from the Diagnostic Interview Schedule, modified to obtain DSM-IV diagnoses.[19]

Follow-up interviews were abbreviated forms of the baseline interview. Participants were asked how many times they had commenced treatment, in any modality, for heroin dependence since the most recent interview, and the time spent in each treatment episode. Current drug use was measured by the OTI. Participants were asked about heroin overdoses and naloxone administration since the previous interview.

Statistical Analyses

For cohort demographics and treatment exposure, means were used to report normally distributed variables and medians for skewed distributions. In comparisons of the cohort with missing cohort members, *t*-tests were used for continuous distributions, and for categorical variables, odds ratios (OR) and 95% confidence intervals (95% CI) were calculated. CIs for population values were calculated for prevalence estimates of annual overdose rates across follow-up. Cochrans' *Q* test was used to examine differences in proportions across follow-up, with the McNemar test for paired proportions used to examine bivariate differences between specific years. Analysis of variances (ANOVAs) with repeated measures were used to compare the continuous variable of polydrug use across the follow-up period and paired *t*-tests used to examine bivariate differences between specific years. When

TABLE 1 Treatment exposure and drug use over 36 months

Treatment exposure	Males ($n = 248$)	Females ($n = 139$)	All ($n = 387$)
Currently in treatment (%)	48.4	59.7	52.5
36-month treatment exposure			
Maintenance (%)	71.0	79.9	74.2
Days in maintenance (median)[a]	546.0	720.0	648.0
Residential rehabilitation (%)	41.7	30.2	37.6
Days in residential rehabilitation (median)[a]	94.0	96.5	94.0
Detoxification (%)	56.5	39.6	50.4
Days in detoxification (median)[a]	10.0	9.0	10.0
Any treatment (%)	98.8	100	99.2
Days in any treatment (median)[a]	386.5	584.0	470.5
Number of treatment episodes (36 months) (median)	3	3	3

[a]Median days enrolled over 36 months of those who enrolled in the treatment modality

TABLE 2 Yearly drug use and nonfatal overdose rates over 36 months

Variable	Baseline (%)	12 months (%)	24 months (%)	36 months (%)	Across follow-up (%)	Analyses
All ($n = 387$)						
Drug use (past month)						
Daily heroin use (%)	78.0	14.2	13.4	13.7	n/a	$Q_3 = 550.0$, $P < 0.001$
Number of other drug classes	3.9	2.7	2.6	1.8	n/a	$F_{1,386} = 436.2$, $P < 0.001$
Cannabis	68.7	48.3	45.5	45.5	n/a	$Q_3 = 109.3$, $P < 0.001$
Methamphetamine	30.2	15.5	15.3	14.2	n/a	$Q_3 = 55.6$, $P < 0.001$
Cocaine	38.0	10.6	6.2	9.0	n/a	$Q_3 = 225.7$, $P < 0.001$
Benzodiazepines	49.1	24.0	21.2	24.0	n/a	$Q_3 = 123.2$, $P < 0.001$
Alcohol	50.4	48.8	50.4	50.9	n/a	$Q_3 = 0.59$, $P > 0.8$
Overdose						
Overdosed	24.3 (20.0–28.6)	10.6 (7.5–13.7)	7.2 (4.6–9.8)	7.0 (4.4–9.5)	18.6 (14.7–22.5)	$Q_3 = 85.5$, $P < 0.001$
Naloxone administered	15.3 (11.7–18.8)	7.0 (4.4–9.5)	4.4 (2.3–6.4)	3.6 (1.8–5.5)	11.9 (8.7–15.1)	$Q_3 = 52.1$, $P < 0.001$
Percent (%) overdosed administered naloxone	62.9	66.0	61.1	51.4	64.0	n/a
Males ($n = 248$)						
Drug use (past month)						
Daily heroin use (%)	78.6	15.3	14.9	14.9	n/a	$Q_3 = 342.6$, $P < 0.001$
Number of other drug classes	3.8	2.7	2.7	1.8	n/a	$F_{1,247} = 117.6$, $P < 0.001$
Cannabis	68.5	50.8	46.0	46.0	n/a	$Q_3 = 63.1$, $P < 0.001$
Methamphetamine	27.4	14.5	15.8	14.5	n/a	$Q_3 = 26.0$, $P < 0.001$

Cocaine	39.9	12.1	8.9			
Benzodiazepines	43.1	25.4	23.0	23.4	n/a	$Q_3 = 46.5$, $P < 0.001$
Alcohol	56.0	54.0	57.7	56.0	n/a	$Q_3 = 1.01$, $P > 0.7$
Overdose						
Overdosed	21.8 (16.6–27.0)	11.7 (7.7–15.7)	8.9 (5.3–12.4)	7.7 (4.3–11.0)	20.2 (15.1–25.2)	$Q_3 = 34.7$, $P < 0.001$
Naloxone administered	14.1 (9.8–18.5)	8.1 (4.7–11.5)	5.7 (2.8–8.5)	3.6 (1.3–6.0)	13.3 (9.1–17.6)	$Q_3 = 24.1$, $P < 0.001$
Percent (%) overdosed administered naloxone	64.7	69.2	64.0	46.8	65.8	n/a
Females ($n = 139$)						
Drug use (past month)						
Daily heroin use (%)	77.0	12.2	10.8	11.5	n/a	$Q_3 = 207.7$, $P < 0.001$
Number of other drug classes	4.0	2.5	2.4	1.7	n/a	$F_{1,138} = 197.7$, $P < 0.001$
Cannabis	69.1	43.9	44.6	44.6	n/a	$Q_3 = 48.5$, $P < 0.001$
Methamphetamine	35.3	17.3	14.4	13.7	n/a	$Q_3 = 31.7$, $P < 0.001$
Cocaine	34.5	7.9	1.4	5.8	n/a	$Q_3 = 91.4$, $P < 0.001$
Benzodiazepines	59.7	21.6	18.0	25.2	n/a	$Q_3 = 85.4$, $P < 0.001$
Alcohol	40.3	39.6	37.4	41.7	n/a	$Q_3 = 0.81$, $P > 0.8$
Overdose						
Overdosed	28.8 (21.2–36.4)	8.6 (3.9–13.4)	4.30 (0.9–7.7)	5.8 (1.8–9.7)	15.8 (9.7–22.0)	$Q_3 = 56.6$, $P < 0.001$
Naloxone administered	17.3 (10.9–23.6)	5.0 (1.4–8.7)	2.2 (0.0–4.6)	3.6 (0.5–6.7)	9.4 (4.5–14.3)	$Q_3 = 32.5$, $P < 0.001$
Percent (%) overdosed administered naloxone	60.1	58.1	51.2	62.1	59.5	n/a

95% CI of population value in brackets

relating earlier to later overdose experience, OR and 95% CI were reported. All analyses were conducted using SPSS for Windows (release 14.0).[20]

RESULTS

Cohort Characteristics

The initial cohort consisted of 615 current heroin users. To ascertain rates and patterns of overdose, the cohort members reported in this study were 387 heroin users who were interviewed at each of the 12-, 24-, and 36-month follow-ups. They consisted of 134 entering MT, 134 entering DTX, 81 entering RRs, and 38 NT subjects. The mean age at baseline was 29.4 years (SD 7.7, range 18–53 years), and 64.1% were male. The cohort had completed a mean of 10.2 years of school education (SD 1.6, range 2–12 years), 30.2% had completed a trade/technical course, and 6.5% a university degree. The main sources of income were: social security allowances (47.0%), criminal activity (20.4%), and wage/salary (18.6%). The median age of first intoxication from any substance was 14.0 years (range 5–34 years), with alcohol (55.8%) and cannabis (40.1%) as the two most common substances. The median age of first heroin use was 18.0 years (range 9–43 years) and median length of heroin use career at entry was 7.0 years (range <1–35 years). Exclusive non-injecting heroin use in the years preceding ATOS enrollment was reported by 9.6% of the cohort.

Before ATOS enrollment, 55.0% had experienced a heroin overdose, 36.7% had overdosed on multiple occasions, and 39.5% had been administered naloxone (Table 1). There were no differences between males and females in lifetime overdose experience (53.2 vs 58.3%), multiple overdoses (36.3 vs 37.4%), or naloxone administration (38.3 vs 41.7%). There were also no gender differences in overdose and naloxone administration in the year preceding ATOS (Table 2).

Importantly, there were no differences between the cohort members included in these analyses and other cohort members in age (29.4 vs 29.0 years), percent male (64.1 vs 69.7%), baseline daily heroin use (78.0 vs 78.4%), lifetime overdose history (55.0 vs 53.1%), or overdose in the preceding 12 months (24.3 vs 26.7%).

Treatment Exposure and Drug Use Over 36 Months

At 36 months follow-up, 52.3% were currently enrolled in a drug treatment program (Table 1). There was widespread exposure across the range of treatment modalities, and multiple treatment episodes were common (Table 1).

Daily heroin use declined dramatically across follow-up ($Q_3 = 550.0$, $P < 0.001$). Daily use declined between baseline and 12 months ($\chi^2 = 230.1$, $P < 0.001$) and then remained stable (Table 1). Similarly, the number of drug classes used (other than heroin) declined across follow-up ($F = 436.2$, $P < 0.001$), with significant declines between baseline and 12 months ($t = 12.9$, $P < 0.001$), and between 24 and 36 months ($t = 11.0$, $P < 0.001$) (Table 1). More specifically, declines were seen in the use of cannabis, methamphetamine, cocaine, and benzodiazepines, but not alcohol (Table 1).

Overdose Over Follow-up

A heroin overdose over follow-up was reported by 18.6% of the cohort, and naloxone had been administered to 11.9% (Table 2). There were no gender differences in the proportions who overdosed or were administered naloxone. There was an overall decline across years in the proportion who overdosed. The

TABLE 3 Previous and subsequent heroin overdoses

Yearly overdoses by follow-up point	Overdosed (%)	Analyses
Baseline—12 months		
Previous overdose (year before ATOS)	26.6	OR 6.3, 95% CI 3.2–12.4
No previous overdose (year before ATOS)	5.5	
12–24 months		
Previous overdose (baseline—12 months)	24.4	OR 5.9, 95% CI 2.5–13.8
No previous overdose (baseline—12 months)	5.2	
24–36 months		
Previous overdose (12–24 months)	32.1	OR 9.0, 95% CI 3.6–22.6
No previous overdose (12–24 months)	5.0	

proportion reporting an overdose in the preceding 12 months declined sharply between baseline and 12 months ($\chi^2 = 31.8$, $P < 0.001$) and then remained stable (Table 2). Similarly, there was an overall decline across follow-up in the proportion having been administered naloxone. Again, the decline occurred between baseline and 12 months ($\chi^2 = 15.0$, $P < 0.001$), with the proportion remaining stable over subsequent years. Overdoses and naloxone administration declined among both males and females. Among those who had used heroin in a particular year, reported annual rates of overdose among non-injectors were lower than among injectors: baseline (5.4 vs 26.3%), 12 months (0.0 vs 13.4%), 24 months (0.0 vs 11.5%), and 36 months (0.0 vs 11.5%).

It is important to note that there were no differences between the annual overdose rates of cohort members included in this study and those of the whole cohort interviewed at each follow-up point (12 months: 10.6 vs 12.3%, 24 months: 7.2 vs 7.3%, 36 months: 7.0 vs 7.0%).

Previous and Subsequent Overdose

Previous overdose experience was strongly related to the likelihood of overdose over follow-up. Those with a history of overdose before ATOS were significantly more likely to have overdosed over follow-up than those without a history of overdose (26.3 vs 9.2%, OR 3.5, 95% CI 1.9–6.4). There was a strong and persistent association between overdose experience in any 1 year and an increased probability of overdose in the subsequent year (Table 3).

DISCUSSION

This is the first study to examine long-term trends in nonfatal heroin overdose. Compared to the year preceding ATOS, rates of heroin overdose remained substantially lower in all subsequent years. Commensurate with heroin use patterns, however, declines in both overdose and naloxone administration were only seen in the first 12 months. After this, rates remained constant. Despite the generally lower overdose rates over the follow-up period, after 3 years, one in five had experienced an overdose, and one in ten had overdosed on more than one occasion.

Perhaps the most important clinical finding from this study was that overdose remained strongly related to previous overdose experience. Three quarters of those who overdosed subsequent to ATOS enrollment had a previous overdose history. More particularly, if a person overdosed in 1 year, they were at substantially greater risk of overdosing again in the next year. Between a quarter and a third of those who

overdosed in a year overdosed again in the subsequent year. This has great clinical significance in terms of both risk and individual clinical management. Repeated overdoses place the person at greater risk of long-term physical and cognitive damage.[3] Given that approximately 1 in 20 overdoses result in death,[2] cumulative risk of death increases with each successive overdose. From the clinical perspective, these data show that there are clear patterns in overdose. Regular screening for overdose by treatment and other agencies will identify those who are at particular risk of an overdose in the near future. Previous research has shown, however, that the experience of an overdose does not significantly raise risk perception about subsequent overdose.[6] Clearly, a major clinical concern would be to raise the awareness of future overdose among those who have recently overdosed.

This was a cohort exposed to substantial treatment over 36 months, as reflected in the sustained lower annual rates of drug use and overdose across follow-up. Would an overdose increase the risk of a subsequent overdose among an untreated population? While the overall overdose rates clearly would remain at higher levels in the absence of treatment, there is reason to believe that such a pattern would emerge. Indeed, consistent with this, those with a history of overdose before ATOS were significantly more likely to overdose over follow-up, and the risk of overdose in the first year *after* ATOS enrollment was substantially higher if an overdose had occurred in the year *before* ATOS.

In interpreting the results of this study, several caveats must be borne in mind. First, to examine the annual trends in overdose, only those who were interviewed at all three annual follow-up points were analyzed. Care should clearly be taken in extrapolating to the broader cohort, as this group may be a more functional subgroup. As noted, however, there were no major differences between these members and others in age, gender, or heroin use. More importantly, from the perspective of this study, there were no differences in overdose histories. There may, however, be other variables relating to overdose risk that were not examined. Care should also be taken in extrapolating to the broader population of heroin users. In particular, entry into the ATOS cohort, as with all cohorts, required the provision of contact details. This may well exclude the more chaotic, less stably housed heroin user. Those recently imprisoned were also excluded. It should be noted, however, that the major demographic characteristics and drug use histories of the cohort were similar to those reported for other cohorts of heroin users.[21,22] Because of long administrative delays in processing deaths in the National Death Index, we had no data at the time of writing on causes of death among cohort members, and the number of fatal overdoses was thus unknown.

In summary, while overdose rates declined compared to baseline, substantial proportions continued to overdose each year, and this was strongly associated with previous overdose history. This is the first study to have examined long-term trends in nonfatal heroin overdose and demonstrates a degree of predictability to overdose. Screening for recent overdose experience appears justified to identify those at greatest risk of subsequent overdose.

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