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Predictors of non-fatal overdose among a cohort of polysubstance-using injection drug users

Thomas Kerr[a,b,*], Nadia Fairbairn[a], Mark Tyndall[a,b], David Marsh[a,c], Kathy Li[a], Julio Montaner[a,b], Evan Wood[a,b]

[a] *British Columbia Centre for Excellence in HIV/AIDS, St. Paul's Hospital, 608–1081 Burrard Street, Vancouver, BC, Canada V6Z 1Y6*
[b] *Department of Medicine, University of British Columbia, 608–1081 Burrard Street, Vancouver, BC, Canada V6Z 1Y6*
[c] *Vancouver Coastal Health, 200–520 West 6th Avenue, Vancouver, BC, Canada V5Z 4H5*

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Abstract

Background: Non-fatal overdose is a major determinant of morbidity among injection drug users (IDU). We sought to evaluate factors associated with non-fatal overdose among IDU in Vancouver.
Methods: We examined non-fatal overdose among participants in the Vancouver Injection Drug Users Study. Correlates of non-fatal overdose occurring between 1996 and 2004 were identified using generalized estimating equations (GEE).
Results: There were 1587 participants included in this analysis, including 576 (36%) women. At baseline, 750 (47%) reported a history of non-fatal overdose. In total, 985 reports of non-fatal overdose were made during follow-up by 519 (32.7%) participants. In multivariate GEE analyses, factors independently associated with non-fatal overdose included: heroin injection (AOR = 2.67), cocaine injection (AOR = 2.01), benzodiazepine use (AOR = 2.00), requiring help injecting (AOR = 1.58), binge drug use (AOR = 1.52), homelessness (AOR = 1.38), alcohol use (AOR = 1.32), street injecting (AOR = 1.22), non-injectable opiate use (AOR = 1.16), speedball use (AOR = 1.15), and recent incarceration (AOR = 1.14). Younger age (AOR = 0.99) and methadone use (AOR = 0.51) were protective.
Conclusions: We found that non-fatal overdose was common among local IDU. Non-fatal overdose was associated with several factors that may be amenable to intervention, including opiate and stimulant use, and the characteristic of requiring help with injecting. These findings indicate the need for the ongoing development of structural interventions to address this common cause of morbidity among IDU.

Keywords: Non-fatal overdose; Injection drug users

1. Introduction

Illicit drug-related overdose has been recognized as a major determinant of morbidity and mortality among injection drug users (IDU) (Wood et al., 2003; Davidson et al., 2003; Warner-Smith et al., 2002). In many countries, fatal overdose is a leading cause of death among IDU, and in response a variety of overdose prevention initiatives have been implemented (Tyndall et al., 2001; Perucci et al., 1991).

Despite being far more common than fatal overdose, non-fatal overdose has received considerably less attention in the scientific literature (Darke et al., 2003). Among IDU participating in studies in Australia and the UK, approximately 30% reported having experienced a non-fatal overdose in the preceding 12 months, and 17% of opiate users in a recent Canadian study reported a non-fatal overdose in the previous 6 months (Bennett and Higgins, 1999; Warner-Smith et al., 2002; Fischer et al., 2004). Non-fatal overdose is an important cause of morbidity among IDU and can result in a number of medical complications, including aspiration pneumonia, hypoxic brain injury, rhabdomyolysis, and renal failure (Darke and Hall, 2003).

Previous studies of non-fatal overdose have typically focused on opiate users, with few studies examining non-fatal overdose related to cocaine use (Kaye and Darke, 2004). Studies of non-fatal overdose where polysubstance-use is prevalent are lacking, as are longitudinal analyses of non-fatal overdose (Darke and Hall, 2003). Further, while fatal overdose has been identified as a leading cause of death among IDU in Vancouver (Tyndall et

* Corresponding author. Tel.: +1 604 806 9116; fax: +1 604 806 9044.
E-mail address: tkerr@cfenet.ubc.ca (T. Kerr).

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al., 2001), there have been few studies of non-fatal overdose in this setting where polysubstance use, including cocaine injection and use of diverted pharmaceuticals, is common (Kerr et al., 2005). Therefore, we investigated factors associated with non-fatal overdose among IDU participating in a prospective cohort study in Vancouver during the years 1996–2004.

2. Methods

The Vancouver Injection Drug Users Study (VIDUS) is a prospective study of injection drug using individuals who have been recruited through self-referral and street outreach from Vancouver's Downtown Eastside since May 1996. The cohort has been described in detail previously (Wood et al., 2001; Tyndall et al., 2003). Briefly, persons were eligible if they had injected illicit drugs at least once in the previous month and resided in the greater Vancouver region. At baseline and semi-annually, subjects provide blood samples and complete an interviewer-administered questionnaire. The questionnaire elicits demographic data as well as information about drug use, HIV risk behavior, and enrollment into addiction treatment. All participants provide informed consent and are given a stipend Can$20 at each study visit. The study has been approved by the University of British Columbia's Research Ethics Board.

The present analyses included all participants who were enrolled between May 1, 1996 and May 30, 2004. The primary endpoint in this analysis was self-reported non-fatal overdose during the previous 6 months. In light of the fact that polysubstance injection drug use is the norm in our setting, and because we were interested in overdoses involving various substances, we used a broad definition of non-fatal overdose. Study participants were simply asked to indicate whether or not they had experienced an overdose in the past 6 months. This definition was successfully piloted during questionnaire development.

Explanatory variables of interest in this analysis included sociodemographic information: sex, age, and homelessness (yes/no). Drug use variables considered refer to behaviors in the past 6 months and included: years injecting; heroin, cocaine, morphine, and speedball injection; crack smoking; benzodiazepine use; non-injection use of opiates; alcohol use of greater than four drinks per day (yes/no); street injecting; requiring help with injecting; and binge injection drug use. As in previous analyses, binge drug use refers to periods in the previous 6 months in which drugs were injected more than usual (Kerr et al., 2005). Other characteristics considered included: incarceration in the past 6 months, being denied access to drug treatment in the previous 6 months, and current methadone treatment (i.e., as opposed to illicitly obtained methadone).

As a first step, we examined rates of overdose during follow-up. The rate presented is the proportion of individuals who reported experiencing a non-fatal overdose during follow-up as a proportion of all individuals followed at that visit. Next, we examined univariate associations between all potential explanatory variables and self-reported history of non-fatal overdose at baseline using Pearson's Chi-square test and the Wilcoxon rank sum test. Since analyses of factors potentially associated with non-fatal overdose use during follow-up included serial measures for each subject, we used generalized estimating equations (GEE) for binary outcomes with logit link for the analysis of correlated data to determine which factors were independently associated with reporting a non-fatal overdose throughout the 85-month follow-up period (Lee et al., 2007). These methods provided standard errors adjusted by multiple observations per person using an exchangeable correlation structure. Therefore, data from every participant follow-up visit were considered in this analysis. For instance, an individual participant may have had non-fatal overdoses and periods without overdoses at several different points during follow-up, and this approach serves to examine behaviors and characteristics that correlated with times when non-fatal overdoses did or did not occur within individuals and between individuals. This approach is commonly used for studies in which a repeated measure binary dependent variable is used in longitudinal studies, and has been used successfully in previous studies examining correlates of drug treatment access in prospective cohort studies of IDU (Shah et al., 2000).

Variables potentially associated with non-fatal overdose were examined in bivariate GEE analyses. In order to adjust for potential confounding, we also fit a multivariate logistic GEE model using an *a priori* defined model building protocol of adjusting for all variables that were statistically significant at the $p < 0.10$ level in bivariate analyses. To consider whether the removal, over time, of individuals who died of a fatal overdose introduced bias into our results, we performed a second multivariate GEE model that excluded all individuals who died of a fatal overdose during follow-up. We also ran sub-analyses that were restricted to individuals with at least two follow-up visits and to individuals with ≤ 2 non-fatal overdose events.

All statistical analyses were performed using SAS software Version 8.0 (SAS, Cary, NC). All p-values are two-sided.

3. Results

In total, 1587 participants were recruited into the VIDUS cohort between May 1, 1996 and May 30, 2004, of whom 1011 (63.7%) were male and 576 (36.3%) were female. The median age at baseline was 33.4 years (IQ range: 25.7–40.1). Overall, these participants contributed to 12,030 observations during the follow-up period and the median number of follow-up visits was 9 (interquartile range: 4–13). In total, 985 non-fatal overdoses were reported by 519 (32.7%) participants. The median number of non-fatal overdoses during follow-up was 1.0 (IQ range: 1–2). As indicated in Fig. 1, the proportion of participants reporting a non-fatal overdose has declined steadily since enrollment, with 21% of individuals reporting a non-fatal overdose in 1997 compared with just 6% in 2004. The most substantial decline occurred during 2001, with the proportion of participants reporting a non-fatal overdose declining from 12 to 5% during this year.

At baseline, 750 (47%) participants reported ever having a non-fatal overdose in the past. Factors positively associated with non-fatal overdose at baseline are shown in Table 1 and include: years of injecting, female gender, and recent incarceration. HIV positivity was marginally associated with non-fatal overdose.

Factors positively associated with non-fatal overdose in univariate GEE analyses are shown in Table 2 and include: age, homelessness, recent incarceration, heroin injection, cocaine injection, speedball injection, morphine injection, benzodiazepine use, non-injection opiate use, binge drug use, speedball injection, alcohol use, requiring help injecting, public injecting, and being denied addiction treatment. Methadone use was inversely associated with non-fatal overdose.

Factors associated with non-fatal overdose in the multivariate GEE analysis are shown in Table 2 and include: age

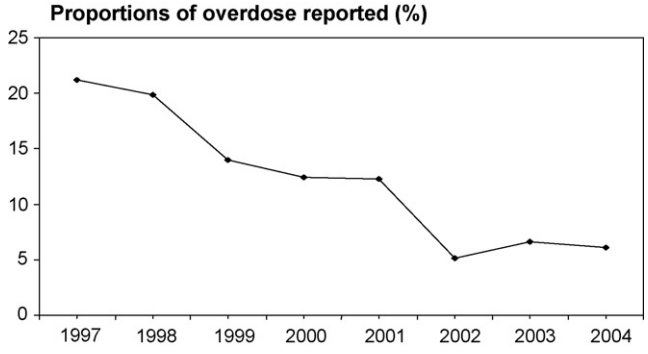

Fig. 1. Rates of non-fatal overdose among VIDUS participants: 1997–2004.

Table 1
Characteristics associated with non-fatal overdoses among a sample of injection drug users in Vancouver

Characteristic	Non-fatal overdose *n* (%) *n* = 837	No overdose *n* (%) *n* = 750	Odds ratio (95% CI)
Age			
Median (IQ range)	33.85 (26.28–40.73)	33.00 (25.23–39.50)	1.01 (0.99–1.02)
Years injecting			
Median (IQ range)	12 (5–23)	7.00 (2–16)	1.04 (1.03–1.05)
Gender			
Male	504 (60.22)	507 (67.60)	
Female	333 (39.78)	243 (32.40)	1.38 (1.12–1.69)
Aboriginal ethnicity			
No	606 (72.40)	554 (73.87)	
Yes	231 (27.60)	196 (26.13)	1.08 (0.86–1.35)
HIV-positive			
No	579 (69.18)	552 (73.60)	
Yes	258 (30.82)	198 (26.40)	1.24 (0.99–1.55)
Residing in DTES[†]			
No	354 (42.29)	319 (42.53)	
Yes	483 (57.71)	431 (57.47)	1.01 (0.83–1.23)
Incarceration[†]			
No	539 (64.40)	520 (69.33)	
Yes	298 (35.60)	230 (30.67)	1.24 (1.00–1.55)

(AOR = 0.99, 95%CI: 0.98–0.99), heroin injection (AOR = 2.67, 95%CI: 2.30–3.10), benzodiazepine use (AOR = 2.00, 95%CI: 1.77–2.26), cocaine injection (AOR = 2.02, 95%CI: 1.76–2.31), requiring help injecting (AOR = 1.58, 95%CI: 1.39–1.79), binge drug use (AOR = 1.46, 95%CI: 1.27–1.69), being denied addiction treatment (AOR = 1.43, 95%CI: 1.24–1.66), homelessness (AOR = 1.38, 95%CI: 1.18–1.61), alcohol use (AOR = 1.32, 95%CI: 1.09–1.60), public injecting (AOR = 1.22, 95%CI: 1.06–1.41), incarceration (AOR = 1.14, 95%CI: 1.01–1.28), and non-injectable opiate use (AOR = 1.16, 95%CI: 1.03–1.31). Methadone use was negatively associated with non-fatal overdose (AOR = 0.51, 95%CI: 0.44–0.59). The GEE model was identical when we excluded all individuals who died of a fatal overdose during follow-up (data not shown). When we restricted our model to individuals with at least two follow-up visits, our model was largely unchanged, with the following variables remaining positively associated with non-fatal overdose: heroin injection, benzodiazepine use, cocaine injection, non-injectable opiate use, alcohol use, requiring help injecting, binge drug use, being denied addiction treatment, homelessness, public injecting, and incarceration. Methadone use remained negatively associated with non-fatal overdose. When we restricted our model to individuals with $\leq$2 non-fatal overdose events, our model was again largely unchanged, with the following variables remaining positively associated with non-fatal overdose: heroin injection, benzodiazepine use, cocaine injection, requiring help injecting, binge drug use, alcohol use, homelessness, and being denied addiction treatment. Non-injection opiate use was marginally ($p = 0.061$) and positively associated with non-fatal overdose, while methadone use remained negatively associated with non-fatal overdose (details available from the corresponding author).

4. Discussion

In the present analysis, we found that non-fatal overdose was common among local IDU, with approximately half reporting a history of non-fatal overdose at baseline and one-third reporting a non-fatal overdose during follow-up. Non-fatal overdose was independently and positively associated with various factors considered, and was, as expected, most strongly associated with specific forms of drug use, including daily heroin and cocaine injection, binge drug use, and benzodiazepine use. Other factors positively associated with non-fatal overdose included requiring help with injections, homelessness, alcohol use, non-injection opiate use, recent incarceration, public injecting, age, and being denied addiction treatment. Interestingly, methadone maintenance therapy was the only variable considered that was inversely associated with non-fatal overdose.

While half of the IDU participating in this study reported a history of non-fatal overdose, it is interesting to note that one-third reported a non-fatal overdose during follow-up. Previous cross-sectional studies typically have found that approximately 30% of IDU report having experienced a non-fatal overdose in the previous year (Bennett and Higgins, 1999; Warner-Smith et al., 2002; Fischer et al., 2004). The present study suggests that this proportion may not change greatly with time, with approximately a third of the IDU population remaining susceptible to non-fatal overdose over several years of follow-up. This is consistent with the findings in this paper that longer years of injecting was associated with increased rates of non-fatal overdose, and suggests that risk of non-fatal overdose is not limited to the beginning of an injecting career but persists throughout the period of injection use. However, it should be noted that there was a decline over time in the proportion of participants

Table 2
Unadjusted and adjusted odds ratios for predictors of non-fatal overdoses among injection drug users

Characteristic	Unadjusted odds ratio (95% CI‡)	*p*-value	Adjusted odds ratio (95% CI‡)	*p*-value
Older age				
Per year older	0.98 (0.97–0.99)	<0.001	0.99 (0.98–0.99)	0.046
Gender				
Female vs. male	1.11 (0.98–1.26)	0.089	1.11 (0.96–1.28)	0.158
Homeless				
Yes vs. no	1.71 (1.49–1.96)	<0.001	1.38 (1.18–1.61)	<0.001
Incarceration†				
Yes vs. no	1.46 (1.32–1.62)	<0.001	1.14 (1.01–1.28)	0.027
Years injecting				
Yes vs. no	1.00 (0.99–1.01)	0.516	–	–
Heroin injection†				
Yes vs. no	4.45 (3.89–5.09)	<0.001	2.67 (2.30–3.10)	<0.001
Cocaine injection†				
Yes vs. no	3.43 (3.03–3.88)	<0.001	2.02 (1.76–2.31)	<0.001
Speedball injection†				
Yes vs. no	2.57 (2.31–2.87)	<0.001	1.15 (1.00–1.32)	0.047
Morphine injection†				
Yes vs. no	1.84 (1.56–2.17)	<0.001	1.01 (0.84–1.22)	0.878
Crack cocaine smoking†				
Yes vs. no	0.99 (0.88–1.11)	0.887	–	–
Benzodiazepine use†				
Yes vs. no	2.50 (2.25–2.76)	<0.001	2.00 (1.77–2.26)	<0.001
Non-injection opiate use†				
Yes vs. no	1.86 (1.67–2.06)	<0.001	1.16 (1.03–1.31)	0.014
Binge drug use†				
Yes vs. no	2.42 (2.20–2.66)	<0.001	1.52 (1.36–1.70)	<0.001
Alcohol use†				
Yes vs. no	1.37 (1.16–1.63)	<0.001	1.32 (1.09–1.60)	0.004
Requires help injecting†				
Yes vs. no	2.50 (2.24–2.78)	<0.001	1.58 (1.39–1.79)	<0.001
Public injecting†				
Yes vs. no	1.89 (1.67–2.14)	<0.001	1.22 (1.06–1.41)	0.005
Methadone				
Yes vs. no	0.57 (0.50–0.65)	<0.001	0.51 (0.44–0.59)	<0.001
Denied treatment†				
Yes vs. no	2.08 (1.84–2.35)	<0.001	1.46 (1.27–1.69)	<0.001

reporting non-fatal overdose, with the most substantial decline occurring during 2001. This decline is consistent with other reports indicating a reduction in heroin-related overdoses during this period (Wood et al., 2006) and suggests that global reductions in heroin supply may have played a role in the declines in non-fatal overdose reported here. It may also be related to the protective effect of methadone treatment and the significant expansion of methadone treatment availability which occurred in British Columbia from 1995 to 2004 (Anderson and Warren, 2004).

Many of our findings are consistent with previous studies. In particular, the use of opiates, alcohol, non-injectable opiates, and benzodiazepines has been associated with overdose among IDU in several settings (Coffin et al., 2003; Sergeev et al., 2003). These substances are central nervous system depressants and therefore increase risk for overdose, especially when used in combination. The findings pertaining to non-injectable opiates and benzodiazepines suggest that pharmaceutical and non-injection drug use plays a role in determining overdose locally, despite previous findings suggesting that the risk for overdose is significantly reduced when opiates and other illicit drugs are consumed through routes other than injection (Brugal et al., 2002; Darke and Hall, 2003). However, this finding may also be explained by polydrug use in which benzodiazepines, etc., are being used in conjunction with heroin or other injectable drugs (Coffin et al., 2003).

The association between morphine and non-fatal overdose may be in part due to the difficult route of administration. Mor-

phine is often injected by crushing up and diluting tablets, and injection of opioid analgesic tablets has also been observed as a risk factor for fatal overdose because injection route of administration involves near instantaneous saturation of central opiate receptors as compared to more gradual saturation when taken orally (Kintz, 2001, 2001). Additionally, due to the high first-pass metabolism of these drugs, tablets intended for oral consumption are typically of higher doses than necessary to induce the same effects via injection, further increasing risk for overdose (Kintz, 2001, 2002). The finding of an independent association of cocaine injection with overdose is perhaps unique, with cocaine-related overdose among IDU having received only limited attention (Kaye and Darke, 2004). This result is not surprising in this context, however, given the prevalence of cocaine injection among local IDU and the high purity of cocaine locally (Kerr et al., 2003).

Homelessness was also strongly and independently associated with overdose in this study. This finding is consistent with another Canadian study (Fischer et al., 2004), and may be explained by more intense patterns of drug use among homeless individuals (Fischer et al., 2004). Indeed, homelessness has been recognized as a major determinant of poor health among IDU (Galea and Vlahov, 2002). This finding may also be explained by a heightened risk for overdose due to rushed injecting in public spaces (Broadhead et al., 2002; Dovey et al., 2001). This latter explanation could also account for the observed association between public drug use and overdose in this study. In order to avoid confrontations with police and others, individuals injecting in public spaces are known to rush their injections, often failing to first "taste" drugs to determine their strength. This in turn can result in too much of the drug being administered and may eventually lead to an overdose event (Brugal et al., 2002). A similar dynamic may explain the observed association between the characteristic of requiring help with injections and overdose. In these instances, the individuals receiving injections have little control of dosing, which can lead to too much of the drug being injected.

Being denied addiction treatment was also associated with overdose in this study. This is concerning, given that participation in addiction treatment has been shown previously to have a protective effect against overdose (Brugal et al., 2005; Caplehorn et al., 1996; Fugelstad et al., 1995). However, in one study, recent participation in abstinence-focused drug treatment was associated with an increased likelihood of having a non-fatal overdose (Fischer et al., 2004). This result was perceived to reflect the reduced tolerance among treatment participants and their heightened risk for overdose upon returning to drug use. In the present study, receiving methadone treatment was the only variable negatively associated with non-fatal overdose, suggesting a protective effect for this particular form of addiction treatment. This is consistent with published studies showing that methadone maintenance treatment is strongly protective against fatal overdose (Van Ameijden et al., 1999). The findings of an association between overdose and recent incarceration are also consistent with previous studies and may be explained by the fact that although individuals recently released from prison may have consumed drugs in prison, they have likely done so with less frequency, and therefore their tolerance may be substantially reduced (Brugal et al., 2002).

These findings indicate the need for additional interventions to reduce the suffering and morbidity associated with non-fatal overdose locally. A recent study suggested that the establishment of safer injection facilities in Germany has been associated with decreased rates of fatal overdose (Poschade et al., 2003). A safer injection facility (SIF), where IDU can inject under medical supervision, has recently opened in Vancouver, although the impact of this facility on overdose has not yet been evaluated (Wood et al., 2004a). However, individuals are currently prohibited from receiving assistance with injections in the facility. Therefore, individuals who require assistance with injections are systematically denied access to the supervision and emergency response to overdose within the SIF. Given the findings observed in this study and elsewhere, the continued expansion of drug treatment options may also help to reduce the incidence of overdose (Fugelstad et al., 1995; Van Ameijden et al., 1999; Brugal et al., 2002), especially given recent evidence indicating barriers to access to addiction treatment locally (Wood et al., 2004a,b, 2005). It has also been suggested that educational programs aimed at informing IDU of the many risk factors for overdose, such as poly drug use, may help to increase awareness (Darke and Hall, 2003; McGregor et al., 2001). As well, it has been suggested that medical practitioners be made aware that prescription drugs such as benzodiazepines may increase risk for overdose (Darke and Hall, 2003). However, the limitations of education-based overdose prevention programs have been highlighted previously, with critics suggesting that these programs fail to consider the social and contextual factors that drive risks such as polysubstance use (Moore, 2004). Such criticisms have led to the call for structural interventions that modify the broader risk environment of IDU (Moore, 2004; Rhodes, 2002), including the provision of supportive housing, which is relevant to the present analysis, given the observed association between homelessness and overdose. Finally, a limited number of cities have implemented take-home naloxone programs for IDU (Seal et al., 2003). Naloxone is an opiate antagonist that reverses the effects of opiates that lead to overdose, including sedation and respiratory depression (Strang et al., 1996). Naloxone programs are attractive due to the fact that naloxone has little or no abuse potential, can be stored for future use, and is easily administered (Strang et al., 1996). However, some concerns about naloxone programs have been expressed, including legal issues related to physicians prescribing an agent that may be administered to someone other than the individual to whom the drug was prescribed (Ashworth and Kidd, 2001). As well, naloxone has a short half-life, and there is risk that individuals may return to their previous sedated state if the half-life of naloxone is shorter than that of the opiate injected (Rosenberg et al., 2002). Lastly, these programs will have little impact on cocaine-related overdose. Given the present findings indicating significant relationships between opiate use and overdose, naloxone distribution is worthy of further investigation.

The present study has several limitations. First, VIDUS is not a random sample, and therefore these findings may not generalize to other IDU populations. Second, our overdose events were

self-defined by study participants who were asked to indicate whether or not they had experienced an overdose in the past 6 months. While this approach may introduce an element of subjectivity into the definition of overdose, we feel that it offers advantages in our setting, where polysubstance use is the norm and where overdoses involving substances other than opiates are common. While definitions of overdose have been used in previous studies, these definitions, particularly those used for cocaine-related overdoses, also introduce limitations related to recall bias and do not ultimately provide a hard diagnosis of overdose. Fourth, the statistical method used considers associations between non-fatal overdose and various independent variables over time. The exact temporal relationship between the outcome of interest and the independent variables could not be ascertained and therefore this study does not allow for a thorough investigation of causal relationships (Deitze et al., 2005).

Lastly, although it has been suggested that changing drug purity may play a role in predicting overdose (Darke et al., 1999), we were unable to consider this factor in the present study.

In summary, we found that many IDU participating in this study had reported experiencing a non-fatal overdose during the study period. Several factors considered were strongly associated with non-fatal overdose, including heroin and cocaine injection, benzodiazepine use, binge drug use, and the characteristic of requiring help with injections. Participation in methadone maintenance therapy had a strong protective effect against overdose. Since many of these risk factors are amenable to intervention, these findings suggest that additional interventions are needed to reduce the morbidity associated with non-fatal overdose in this setting.

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