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Non-fatal overdose as a risk factor for subsequent fatal overdose among people who inject drugs

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ABSTRACT

Objectives: To examine the relationship between non-fatal overdose and risk of subsequent fatal overdose.
Methods: We assessed risk factors for overdose death among two prospective cohorts of persons who inject drugs (PWID) in Vancouver, Canada. Extended Cox regression was used to examine if reports of non-fatal overdose were associated with the time to fatal overdose while adjusting for other behavioral, social and structural confounders.
Results: Between May, 1996 and December, 2011, 2317 individuals were followed for a median of 60.8 months. In total, 134 fatal overdose deaths were identified for an incidence density of 8.94 (95% confidence interval [CI]: 7.55–10.59) deaths per 1000 person-years. During the study period there were 1795 reports of non-fatal overdose. In a multivariate model, recent non-fatal overdose was independently associated with the time to overdose mortality (adjusted hazard ratio [AHR] = 1.95; 95% CI: 1.17–3.27). As well, there was a dose response effect of increasing cumulative reports of non-fatal overdose on subsequent fatal overdose.
Conclusion: Reports of recent non-fatal overdose were independently associated with subsequent overdose mortality in a dose-response relationship. These findings suggest that individuals reporting recent non-fatal overdose should be engaged with intensive overdose prevention interventions.

1. Introduction

Globally, the nonmedical use of drugs represents a considerable public health burden and the human and financial costs have been a growing focus of research over the past decade. Of all the harms associated with illicit drug use, among the most direct and important consequences is fatal overdose. In the United States, for instance, accidental overdose has recently emerged as a leading cause of death (Mack, 2013; Murphy et al., 2013). Similarly, overdose mortality has been a longstanding concern, particularly among persons who inject drugs (PWID; Mathers et al., 2013; Quan et al., 2011).

In this context, considerable research has been dedicated to identifying risk factors for overdose mortality with many past studies examining toxicology reports and other circumstances of overdose death (Preti et al., 2002; Zamparutti et al., 2011). Similarly, significant energy has gone into identifying risk factors associated with non-fatal overdose (Darke et al., 2005; Mathers et al., 2013). Substantially more common than fatal overdose (Warner-Smith et al., 2002), non-fatal overdoses are the cause of significant morbidity with a proportion of individuals suffering from hypoxia, aspiration or other negative health outcomes (Britton et al., 2010; Warner-Smith et al., 2002, 2001). The reported prevalence of non-fatal overdoses among illicit drug users has varied significantly based on geography and study population, with estimates ranging between 20% and 70% per lifetime (Darke et al., 1996; Kerr et al., 2007; Kinner et al., 2012; Ochoa et al., 2001; Silva et al., 2013).

One important question, which remains insufficiently addressed in the literature, is to what degree non-fatal overdose events are associated with the risk of subsequent fatal overdose. It may be that persons who experience non-fatal overdose may become more cautious in their future drug use thereby reducing the risk of future adverse events (Mathers et al., 2013), or that those experiencing non-fatal overdose are at higher risk of subsequent fatal overdose (Coffin et al., 2007; Stoové et al., 2009). Due to the urgent public health crisis surrounding fatal overdose mortality, the present

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study was undertaken to examine if self-reported non-fatal overdose was associated with subsequent fatal overdose among PWID in a Canadian setting.

2. Methods

Data for the present study were derived from the Vancouver Injection Drug Users Study (VIDUS) and AIDS Care Cohort to Evaluate Access to Survival Services (ACCESS), which are open prospective cohorts of persons who use drugs in Vancouver, Canada. The studies have been described in detail previously and are essentially identical in their recruitment, data collection and follow up procedures with the exception of HIV status and an eligibility criterion regarding injection drug use (Kerr et al., 2008; Strathdee et al., 1998; Wood et al., 2001). HIV-negative adult persons who have injected drugs in the previous month are eligible for VIDUS and HIV-positive adult persons who have used an illicit drug other than cannabinoids in the previous month are eligible for ACCESS. Individuals who become HIV-infected while under follow up in VIDUS are offered recruitment into the ACCESS study.

At baseline and semiannually, participants provide blood samples for serologic testing for HIV and hepatitis C virus and complete an interviewer-administered questionnaire. Participants receive $20CAD for each study visit. The questionnaire items are essentially identical in both studies and elicit demographic data as well as information about drug use, HIV risk behavior, and drug treatment. The studies have been approved by the University of British Columbia/Providence Health Care Research Ethics Board.

The outcome of interest in this analysis was overdose mortality derived from a confidential record linkage with the provincial Vital Statistics Agency, with the provincial Coroner's office and other tracking procedures. The cause of death for each case is coded in accordance with the International Classification of Diseases, Tenth Revision (ICD-10).

The primary explanatory variable of interest was non-fatal overdose in the previous 180 days. As part of the study's baseline and semi-annual follow up questionnaires, participants were queried about recent non-fatal overdose experiences. The question specifically asked: "In the last six months, have you overdosed by accident (i.e., where you had a negative reaction from using too much drugs)?" The questionnaire did not ask participants if they had previously intentionally overdosed. Socio-demographic characteristics and behavioral factors were also considered as secondary explanatory variables. These included: age (per 10 years older), gender (male vs. female), ethnicity (Caucasian vs. other), homelessness (yes vs. no), incarceration (yes vs. no), daily cocaine injection (yes vs. no), daily heroin injection (yes vs. no), daily crack smoking (yes vs. no), enrolment in methadone maintenance treatment (yes vs. no), HIV serostatus (positive vs. negative) and HCV serostatus (positive vs. negative). All behavioral variables referred to the six months prior to the interview and were treated as time-updated. Unless otherwise specified, variable definitions are consistent with those described in previous studies.

The present analyses were restricted to those participants who completed baseline and at least one follow-up visit between May 1996 and December 2011. To avoid potential confounding due to long durations between the last study visit and the date of death, individuals who were deceased more than 24 months after the last follow-up visit were censored on the last follow-up date in December 2011.

As an initial analysis, we summarized the baseline characteristics of participants, stratified by recent non-fatal overdose status at baseline. Comparisons of baseline characteristics for participants with and without report of recent non-fatal overdose were made using the Chi-square test (for binary measures) and Wilcoxon rank sum test (for continuous measures). Overdose mortality rate and 95% confidence interval (CI) were calculated using the Poisson distribution. Deaths from other causes were censored as non-events and treated as competing risks for the occurrence of fatal overdose. Therefore, cumulative incidence function was applied to estimate the cumulative probabilities of fatal overdoes for participants with and without a recent non-fatal overdose at baseline, and the difference between groups was tested using Gray's method (Gray, 1988). Survival probabilities were also estimated using the complement of cumulative incidence function.

We then used extended Cox regression model (Kleinbaum, 1996) to examine bivariate associations between each explanatory variable and time to overdose mortality. To fit the multivariate model, we used a previously described backwards selection process (Maldonado and Greenland, 1993; Rothman et al., 2008). In brief, we began with all explanatory variables of interest in a full model, then generated a series of reduced models by removing each secondary explanatory variable one at a time. For each of these models we assessed the relative change in the coefficient for non-fatal overdose. The secondary explanatory variable that resulted in the smallest absolute relative change in the coefficient for non-fatal overdose was then removed. Secondary variables continued to be removed through this process until the smallest relative change exceeded 5%. Remaining variables were considered confounders and were included in the final multivariate model. As a sub-analysis, we also used extended Cox regression to examine if the number of recent non-fatal overdose events is associated with the time to fatal overdose in a dose-dependent fashion. A multivariate model was used and adjusted for age and hive serostatus. Here, zero overdoses was the reference category and we compared this to individuals having had 1, 2–3, 4–7 and 8 or greater 6-month observation periods where the individual reported at least one overdose during the entire cohort observation period.

All p-values were two-sided. All statistical analyses were performed using SAS software version 9.3 (SAS, Cary, NC).

3. Results

In total, 2598 participants were recruited and followed between May 1996 and December 2011. Overall, 281 (10.8%) individuals were excluded as a result of missing follow-up information or incomplete data. Those participants who were excluded were younger ($p < 0.05$), however, there was no difference in baseline reports of recent non-fatal overdose or any of the other variables considered.

For the 2317 participants eligible for the present study, the median follow up time was 60.8 months (interquartile range: 33.5–112.9). Overall, 319 (13.8%) individuals reported a recent non-fatal overdose at baseline. The baseline characteristics of study participants stratified by fatal overdose are presented in Table 1. As shown, those who died from overdose during follow up were more likely to be HIV and/or HCV seropositive or report daily injection of cocaine at baseline (all $p < 0.05$).

During the study period, 883 participants experienced a total of 1795 times of non-fatal overdose, the overall non-fatal overdose rate is 11.97 (95%CI: 11.21–12.80) events per 100 person-years. Similarly, there were 134 fatal overdoses with a rate of 8.94 (95% CI: 7.55–10.59) deaths per 1000 person-years producing a crude rate ratio between non-fatal overdose and fatal overdose of 13.45.

Fig. 1 presents the cumulative survival probabilities stratified by baseline recent non-fatal overdose. As shown here, the cumulative survival probability among participants reporting a recent fatal overdose was 95.9% by 36 months of follow up compared to 97.9% among participants without reports of recent non-fatal overdose