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The effect of prescription opioid injection on the risk of non-fatal overdose among people who inject drugs

Stephanie Lake[a,b], Kanna Hayashi[a,c], Jane Buxton[b], M.-J. Milloy[a,c], Huiru Dong[a], Evan Wood[a,c], Julio Montaner[a,c], Thomas Kerr[a,c,*]

[a] British Columbia Centre for Excellence in HIV/AIDS, St. Paul's Hospital, 608-1081 Burrard Street, Vancouver, BC V6Z 1Y6, Canada
[b] School of Population and Public Health, University of British Columbia, 2206 East Mall, Vancouver, BC V6T 1Z3, Canada
[c] Department of Medicine, University of British Columbia, St. Paul's Hospital, 608-1081 Burrard Street, Vancouver, BC V6Z 1Y6, Canada

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ABSTRACT

Objectives: Prescription opioid (PO) use by people who inject drugs (PWID) is a growing public health concern. Non-fatal overdose remains a leading source of morbidity among PWID, however, little is known about the relationship between PO injection and non-fatal overdose in this population. In this study we sought to examine the impact of PO injection on non-fatal overdose among PWID from Vancouver, Canada.
Methods: Data were derived from two open prospective cohorts of PWID for the period of December, 2005 to May, 2014. Multivariable generalized estimating equations were used to examine the odds of overdose among those who injected: POs; heroin; and POs and heroin.
Results: In total, 1660 PWID (33.7% women) participated in this study. In multivariable analyses, in comparison to those who were injecting non-opioid drugs, exclusive PO injection was not significantly associated with non-fatal overdose (adjusted odds ratio [AOR]: 1.17, 95% confidence interval [CI]: 0.74–1.86). The odds of non-fatal overdose were elevated for heroin injection (AOR: 1.72, 95% CI: 1.31–2.27), but were greatest for those who injected both heroin and POs (AOR: 2.46, 95% CI: 1.83–3.30).
Discussion: Compared to injecting non-opioids, injecting POs exclusively did not increase risk of non-fatal overdose; however, injecting both POs and heroin doubled the risk. This may reflect consistencies in drug potency and composition when POs are used, as well as unique characteristics of exclusive PO injectors. Our findings call for the continued scale-up of evidence-based overdose prevention interventions for people who inject opioids, including POs.

1. Introduction

An epidemic of opioid-related overdose deaths in North America has followed from substantial increases in the use of prescription opioid analgesics (POs; Centers for Disease Control and Prevention, 2012; Cerda et al., 2013; Manchikanti and Singh, 2008). The use of diverted POs among high-risk substance-using populations, including people who inject drugs (PWID), has also increased (Bruneau et al., 2012; Fischer et al., 2008). While alarmingly high rates of PO injection have been documented in rural areas where access to a range of illicit drugs may be limited (Havens et al., 2007), accounts from urban drug centers have also demonstrated that despite high accessibility of heroin, the availability of diverted POs has also increased (Nosyk et al., 2012). While the association between PO use and accidental overdose in the general public has been well-established (Bohnert et al., 2011; Dart et al., 2015; Fischer et al., 2014), the impact of illicit PO use on overdose among long-term drug users, such as PWID, is not known.

Overdose remains a leading cause of morbidity and mortality among PWID (Degenhardt and Hall, 2012; Miller et al., 2007; Warner-Smith et al., 2002), and is prevalent with roughly 30–45% of PWID having experienced at least one non-fatal overdose in their lifetime (Havens et al., 2011; Kerr et al., 2007; Ochoa et al., 2005; Pollini et al., 2006; Sherman et al., 2007), and as many as 20% reporting a non-fatal overdose in the previous year (Ochoa et al., 2005). The health consequences of non-fatal overdose can be severe and include a range of injuries such as acute hypoxia including neurological (e.g., stroke) and solid organ (e.g., renal failure) concerns (Warner-Smith et al., 2002, 2001). Furthermore, those who have survived an overdose are at a heightened risk for future overdose (Darke et al., 2005; Kinner et al., 2012), including fatal overdose (Stoove et al., 2009). Non-fatal overdose also poses a major

* Corresponding author at: Urban Health Research Initiative, B.C. Centre for Excellence in HIV/AIDS, University of British Columbia, St. Paul's Hospital, 608-1081 Burrard Street, Vancouver, BC V6Z 1Y6, Canada.
E-mail address: uhri-tk@cfenet.ubc.ca (T. Kerr).

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burden on the health care system as a leading reason for emergency department presentation (Palepu et al., 2001), which can result in long term institutionalization among those with severe neurological injuries.

Past research has identified a significant positive association between PO use (i.e., oral, intranasal, or intravenous administration) and non-fatal overdose (Lake et al., 2015), and has also found that among PO-using young adults, non-fatal overdose is more common among those who inject POs (Silva et al., 2013b). However, few studies have explored a potential independent association between PO injection and non-fatal overdose among PWID. While many PWID have long-term experience with heroin injection, the harms associated with PO injection may be perceived as comparatively less threatening: despite similarities in pharmacological effect (Trescot et al., 2008), key differences in the composition and preparation of these two types of drugs may produce different overdose risks. For example, whereas POs are manufactured for licit use and maintain consistent doses and purities, these characteristics may be unpredictable in heroin due to it being unregulated (Werb et al., 2013).

As PO injection becomes more prevalent among high-risk drug using populations, understanding the effect of PO injection is critical to overdose prevention efforts. The present study therefore aims to investigate the effect of PO injection on non-fatal overdose among PWID.

2. Materials and methods

2.1. Study sample

The Vancouver Injection Drug Users Study (VIDUS) and the AIDS Care Cohort to Evaluate Exposure to Survival Services (ACCESS) are ongoing open prospective cohorts of adults who use illicit drugs recruited through self-referral and street outreach in Vancouver, Canada. The cohorts have been described in detail previously (Strathdee et al., 1998). Briefly, VIDUS enrolls HIV-negative people who report injecting an illicit drug at least once in the previous month; ACCESS enrolls HIV-positive people who report using an illicit drug other than cannabis in the previous month. For both cohorts, other eligibility requirements include being aged 18 years or older, residing in the greater Vancouver region and providing written informed consent. All study instruments and follow-up procedures are harmonized, allowing data from both cohorts to be combined into one dataset for analysis.

At baseline and semi-annually thereafter, participants complete an interviewer-administered questionnaire eliciting socio-demographic data as well as information pertaining to drug use, risk behaviours, and health care utilization. Nurses collect blood samples for HIV testing (VIDUS) or disease monitoring (ACCESS), and hepatitis C serology, and also provide basic medical care and referrals to appropriate health care services. Participants received a $30 (CDN) honorarium for each study visit. The University of British Columbia/Providence Health Care Research Ethics Board has provided ethical approval for the study.

2.2. Measures

The present analysis was restricted to participants who completed a baseline questionnaire and at least one follow-up questionnaire between December, 2005 and May, 2014, and who reported active (i.e., previous six month) injection drug use. The outcome of interest was self-reporting experiencing an overdose in the previous six months, which was assessed and recorded at baseline and every follow-up interview over the study period. Consistent with previous work (Kerr et al., 2007; Mitra et al., 2015) participants who responded 'yes' to the question "In the previous six months, have you overdosed by accident (i.e., where you had a negative reaction from using too much drugs)?" were considered recent survivors of non-fatal overdose. PO injection was assessed through the question: "In the last six months, which of the following drugs did you inject?", to which participants were provided a list and pictures of common POs. The list underwent yearly modifications in order to reflect up-to-date trends in the types of illicit POs used. The most recent questionnaire included oxycodone (OxyNeo, OxyContin, Percocet), hydrocodone (Dilaudid), morphine, meperidine (Demerol), methadone, fentanyl, and pentazocine (Talwin). Participants were also given the option of specifying other POs that were not on the list. We then built a four-category primary exposure variable: no opioid injection (i.e., people who inject non-opioid drugs including cocaine or methamphetamine; reference category); PO injection exclusive of heroin injection (category 2); heroin injection exclusive of PO injection (category 3); and co-occurring heroin and PO injection (category 4).

We examined various potential sociodemographic and substance use-related confounders based on previously established associations with non-fatal overdose. Sociodemographic confounders were: age (per year older); gender (male vs. female); ethnicity (Caucasian vs. other); recent homelessness (yes vs. no); and recent incarceration (yes vs. no). Behavioural/drug-related confounders were: length of injection drug use in year (per year longer); binge drug use, defined as using more drugs than usual (yes vs. no); injecting in public (yes vs. no); requiring help injecting (yes vs. no); enrolled in a methadone maintenance program (yes vs. no); heavy alcohol use, defined as >14 drinks per week or >4 drinks on one occasion for men, and >7 drinks per week or >3 drinks on one occasion for women (National Institute on Alcohol Abuse and Alcoholism; yes vs. no); cocaine injection (yes vs. no); methamphetamine use (yes vs. no); benzodiazepine use (yes vs. no); crack smoking (yes vs. no); and non-injection PO use (yes vs. no). Unless otherwise specified, all behavioural and substance use-related variables as well as recent incarceration and recent homelessness refer to events or behaviours that occurred at least once in the previous six months.

2.3. Analysis

First, we examined the univariable relationships between each independent variable and non-fatal overdose using generalized estimating equations (GEEs) with logit link for correlated data (Lee et al., 2007). This method uses an exchangeable correlation structure to provide standard errors adjusted by multiple observations per individual (i.e., multiple follow-up data for each participant), and was chosen given the repeated binary outcome measure. This method has been used successfully in previous non-fatal overdose studies (Kinner et al., 2012; Milloy et al., 2008). Next, we built a full multivariable GEE model that included all variables significantly association with the outcome at $p < 0.10$ in the univariable model. Using a conservative stepwise backward selection approach, we fit a series of reduced models comparing the coefficient value associated with the main explanatory variable in the full model to its corresponding value in each of the reduced models, and dropped the secondary variable associated with the smallest relative change. We continued this iterative process until the minimum change exceeded 5%. All analyses were performed in SAS software version 9.3 (SAS Institute Inc., Cary, NC). All p-values are two-sided.

3. Results

Between December, 2005 and May, 2014, 1660 actively injecting study participants, including 559 (33.7%) women, completed a total 10,919 study visits. Of these 10,919 observations, 233 (2.1%) were removed from the analysis due to invalid or missing values, yielding a total of 10,686 analytic observations. The median number of follow up visits was 5 (interquartile range [IQR]: 2–10). The baseline median age of the sample was 42.1 years (IQR: 35.5–48.0). The proportion of PWID reporting injection of POs during the previous six months ranged from 16.3% to 35.1% (median: 24.5%), with rates peaking between June and November, 2007. Heroin was the most commonly injected opioid, with 30.1–49.3% (median: 40.5%) of PWID reporting exclusive heroin injection in the previous six months and 10.9–29.7% (median: 19.4%) reporting injection of both heroin and POs. A small proportion of PWID (2.7–6.6%) injected POs exclusive of heroin at each follow-up. The median prevalence of non-fatal overdose during each follow-up period was 6.0% (IQR: 4.9–7.1%), with the highest rate being reported at 8.8% between December, 2012 and May, 2013. By the end of the study period, a total of 413 (24.9%) individuals experienced a total of 670 non-fatal overdoses. Table 1 summarizes sample baseline characteristics of the sample, stratified by opioid injection status.

In the final multivariable GEE model adjusted for incarceration, public injecting, assisted injecting, methadone maintenance treatment, heavy alcohol use, and PO non-injection (Table 2, Fig. 1), exclusive PO injection was not independently associated with non-fatal overdose (adjusted odds ratio [AOR]: 1.17, 95% confidence interval [CI]: 0.74–1.86); however, participants who injected heroin but not POs had significantly increased odds of overdosing (AOR: 1.72, 95% CI: 1.31–2.27), and those who injected both heroin and POs exhibited the highest odds of overdosing (AOR: 2.46, 95% CI: 1.83–3.30), compared to those who did not recently inject an opioid. Other factors positively associated with non-fatal overdose in the multivariable model included incarceration (AOR: 1.73, 95%CI: 1.40–2.13), public injecting (AOR: 1.46, 95% CI: 1.20–1.79), requiring help injecting (AOR: 1.51, 95% CI: 1.22–1.88), heavy alcohol use (AOR: 1.30, 95% CI: 1.04–1.62), and non-injection PO use