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Prescription Opioid Use and Non-fatal Overdose in a Cohort of Injection Drug Users

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Abstract

Background—There is growing concern regarding rising rates of prescription drug-related deaths among the general North American population as well as increasing availability of illicitly obtained prescription opioids. Concurrently among people who inject drugs (IDU), illicit prescription opioid use has increased while non-fatal overdose remains a major source of morbidity.

Objectives—This study aimed to evaluate whether the use of POs was associated with non-fatal overdose among IDU in Vancouver, Canada.

Methods—Data was obtained from two open prospective cohorts of IDU between December 2005 and May 2013. We used generalized estimating equation (GEE) logistic regression to evaluate the association between prescription opioid use and non-fatal overdose, adjusting for various social, demographic, and behavioral factors.

Results—There were 1,614 IDU, including 541 (33.5%) women, who were recruited and included in this analysis. At baseline, 526 (32.6%) reported using POs and 118 (7.3%) reported experiencing an overdose in the previous six months. In a multivariable analysis, prescription opioid use remained independently associated with non-fatal overdose (adjusted odds ratio: 1.61, 95% confidence interval: 1.32–1.95), after adjusting for confounders.

Conclusion—We observed relatively high rates of prescription opioid use among IDU in this setting, and found an independent association between prescription opioid use and non-fatal overdose. Our data is likely representative of riskier substance use associated with those who use

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prescription opioids within our sample. Interventions to prevent and respond to overdoses should consider the higher risk profiles of IDU who use prescription opioids.

Keywords

Prescription opioids; Non-fatal overdose; Injection drug use; Opioid analgesics

INTRODUCTION

Prescription opioid use has increased substantially in North America over the past two decades (1–5), with its consumption approaching 80% of the global supply (6). Concurrently, North America has seen a drastic increase in nonmedical prescription opioid use and dependence, leading to an epidemic of opioid-related deaths (3, 7–10). In the US, fatal prescription opioid-related overdoses outnumber those caused by heroin and cocaine combined (8), and have contributed to a death toll exceeding that from motor vehicle accidents (11). Other nations are facing similar challenges. In Canada, for example, the prescription opioid-related death rate in the province of Ontario doubled from 1991 to 2004 (12).

These concerns have coincided with a noted increase in availability of prescription opioids sold illicitly across North America (5, 13). For example, between 2006 and 2010 in Vancouver, there was a steady increase in the availability of aspirin/codeine, hydromorphone, morphine, oxycodone, and acetaminophen/codeine, despite supplies of heroin and cocaine remaining relatively stable (14). These trends are accompanied by an increase in prescription opioid use among street-involved and at-risk individuals, including people who inject drugs (IDU) (15, 16). A national survey found that among opioid users, the prevalence of illicit prescription opioid use surpassed that of heroin use in 5 out of 7 major Canadian cities (17).

Although previous studies have documented high rates of overdose among young people who use prescription opioids (18), little is known about the relationship between prescription opioid use and overdose among polysubstance using adult IDU who have a longstanding experience with intravenous heroin use. While frequent heroin use is a common risk factor for overdose in this setting (19, 20), the use of a similar but regulated substance may mean that users are better able to manage dosing and possibly prevent overdose.

Lifetime prevalence of non-fatal overdose is common among IDU (19), and is associated with a multitude of detrimental health outcomes including peripheral neuropathy, temporary limb paralysis, chest infection, brain injury, renal failure, and seizures (21–23). Given the marked increase in the illicit availability and use of prescription opioids in North America, coupled with an ongoing high rate of non-fatal overdose in IDU, the present study aims to examine the relationship between prescription opioid use and non-fatal overdose among a cohort of polysubstance-using IDU in Vancouver, Canada.

METHODS

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 adult illicit drug users recruited through self-referral and street outreach in Vancouver. The studies have been described in detail previously (24, 25). Briefly, VIDUS enrolls HIV-negative persons who reported injecting an illicit drug at least once in the previous month; ACCESS enrolls HIV-positive persons who reported using an illicit drug other than marijuana in the previous month. For both cohorts, other eligibility criteria included being aged 18 years or older, residing in the greater Vancouver region and providing written informed consent. The study instruments and all other follow-up procedures for each study are essentially identical to allow for combined analyses.

At baseline and semi-annually, participants completed an interviewer-administered questionnaire eliciting socio-demographic data as well as information pertaining to drug use patterns, risk behaviors, and health care utilization. Nurses collected blood samples for HIV testing (for VIDUS participants) or disease monitoring (for ACCESS participants), and hepatitis C serology, and also provided 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 provided ethical approval for the study.

Measures

The present analysis included participants who completed the baseline questionnaire between December 2005 and May 2013 and reported injecting drugs in the previous six months. The outcome of interest was non-fatal overdose, while the primary independent variable was prescription opioid use. Consistent with previous analyses (26), the outcome was based on the following question: “In the last six months, have you ever overdosed by accident (i.e., where you had a negative reaction from using too much drugs)”. We used a general definition of prescription opioid use: participants were considered prescription opioid users as long as they reported using a prescription opioid at least once in the previous six months through any route of administration (i.e. oral, intranasal, intravenous). Two questions assessed prescription opioid use: “In the last six months, which of the following non-injection drugs were you using?” and “In the last six months, which of the following drugs did you inject?” (the answer options for type of prescription opioid were the same for each question). As PO misuse became more common, and as new prescription opioids became available, the questionnaire was modified to include a more comprehensive list. The most recent follow-up (2013) allowed participants to answer “yes” or “no” to OxyNeo, OxyContin, Percocet, morphine, dilaudid, Demerol, methadone, fentanyl, hydrocodone, and talwin. Participants could also specify if any prescription opioid they used was not on the list provided.

Additional confounders, based on their known or *a priori* hypothesized association with non-fatal overdose, were: age (per year older), gender (male vs. female), ethnicity

(Caucasian vs. other), unstable housing (yes vs. no), sex work involvement (yes vs. no), cocaine injection (daily vs. <daily), heroin injection (daily vs. <daily), crack cocaine smoking (daily vs. <daily), benzodiazepine use (yes vs. no), heavy alcohol use (>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 (27); yes vs. no), requiring help injecting (yes vs. no), binge drug use (yes vs. no), incarceration (yes vs. no), addiction treatment (including methadone; yes vs. no), denied access to addiction treatment (yes vs. no), HIV serostatus (positive vs. negative), time since first injection (per year longer), injecting in public (yes vs. no), and depression (CES-D 16 vs. <16; yes vs. no). All behavioral variables refer to the participant's behavior in the six months prior to the interview. Unless otherwise specified, variable definitions are consistent with those described in previous studies (19, 28, 29).

Analysis

We summarized the baseline characteristics of participants, stratified by non-fatal overdose status. Baseline univariable associations between all independent variables and non-fatal overdose were explored using Pearson's Chi-square (for binary measures) and Wilcoxon rank sum tests (for continuous measures).

As multiple measures for outcome variables yielded serial measures for each subject, we used a generalized estimating equation (GEE) with logit link for correlated data to determine which factors were independently associated with non-fatal overdose through the entire follow-up period (30). Using an exchangeable correlation structure, this method provides standard errors adjusted by multiple observations per individual, including data from each participant's follow-up visit(s). This approach serves to examine behaviors and characteristics, including prescription opioid use, captured at baseline and each six-month follow-up period, and evaluate its association with experiencing or not experiencing a non-fatal overdose during the corresponding baseline or follow-up periods throughout the entire study. This approach is often used in longitudinal studies involving a repeated binary measure for the dependent variable, and has been used successfully in studies of non-fatal overdose in IDU (19, 31).

Using GEE, we examined the bivariable associations between each explanatory variable and non-fatal overdose. To fit the multivariable model, we employed a conservative stepwise backward selection approach. Using a model-building protocol defined *a priori*, we included all variables that were significant at $p < 0.10$ in bivariable analysis in the full multivariable GEE model, and used a stepwise approach to fit a series of reduced models (32). Using a method successfully applied in other studies (33), we compared the coefficient value associated with the main explanatory variable of interest (i.e. prescription opioid use) in the full model to the coefficient 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.

RESULTS

In total, 1,614 IDU completed a baseline questionnaire between May 2005 and December 2013, and overall these participants contributed to 9,448 observations. In total, 1,308 (81.0%) individuals returned for at least one follow-up visit, and the median number of follow-up visits was 5 (IQR: 2–9). Table 1 summarizes baseline characteristics of the participants, stratified by non-fatal overdose status. As shown, 541 (33.5%) were female, and baseline median age was 41.6 (interquartile range [IQR]: 35.2–47.5) years old. At baseline, 118 (7.3%) participants reported experiencing a recent non-fatal overdose, while 526 (32.6%) reported recently using prescription opioids. The proportion of participants reporting a recent overdose at baseline or follow-up ranged from 3.9% to 8.6% (median: 5.7%), yielding a total of 558 non-fatal overdose events reported by 356 (22.1%) individuals by the end of the study period. The prevalence of recent PO use at follow-up ranged from 20.0% to 38.1% (median: 27.5%).

Table 2 presents the results of bivariable and multivariable GEE analyses with a summary of unadjusted and adjusted associations with non-fatal overdose. In multivariable analysis, after adjustment for potential confounders, prescription opioid use remained independently and positively associated with non-fatal overdose (adjusted odds ratio [AOR]: 1.61, 95% Confidence Interval [95%CI]: 1.32–1.95). Other variables that were associated with non-fatal overdose were daily heroin injection (AOR: 1.38, 95% CI: 1.10–1.73), recent incarceration (AOR: 1.88, 95% CI: 1.52–2.33), requiring help injecting (AOR: 1.55, 95% CI: 1.23–1.94), and injecting in public (AOR: 1.64, CI: 1.32–2.04).

DISCUSSION

Our results show that prescription opioid use was common, with approximately one-quarter of participants reporting using a prescription opioid in the most recent follow-up visit. We also found that PO use is significantly and positively associated with non-fatal overdose after controlling for potential confounders.

Considering prevalence estimates of approximately 5% among the general Canadian population in 2009 (34), the presently recorded rates of non-medical prescription opioid use are—as might be expected given the nature of the sample—high by comparison. However, the observed rates are still only roughly one-third that of prescription opioid injection among a sample of hepatitis C negative IDU in Montreal from 2009 (15). This difference might be rooted in the long history of extensive heroin use and availability in Vancouver's Downtown Eastside, and consequently lower demand for alternatives to heroin compared to other major cities.

The relationship between prescription opioid injection and non-fatal overdose has been detected in rural drug-using populations, where heroin supply is sparse (35). However, previous cross-sectional research of urban opioid users found no significant association between prescription opioid use and non-fatal overdose (36, 37). This is inconsistent with our results, which add a longitudinal perspective to the issue, and suggest that urban IDU who use prescription opioids are in fact at a higher risk of non-fatal overdose. Our result is,

however, somewhat consistent with the previously noted increased risk of non-fatal overdose associated with morphine injection (20) and opioid non-injection (18–20, 38).

Our finding may be explained through various pathways. Notably, another Canadian study found that people who used prescription opioids were more likely to report using benzodiazepines and cocaine (36), both of which are well-documented risk factors for overdose, especially when used concurrently with opioids (19, 37, 39–44). While neither benzodiazepine use nor daily cocaine use was significantly associated with non-fatal overdose in our study, it is plausible that the people who use prescription opioids in our sample have a more complex polysubstance profile than those who do not. In this sense, polysubstance use—which has been previously shown to predict overdose (41, 44, 45)—might be the underlying risk factor in the presently observed association.

Our finding might also be explained by engagement in other high-risk injecting behaviors, such as increased injection frequency and injecting in public. These behaviors have been recorded previously among people who inject POs (15, 46), and their associated overdose risks have been demonstrated in our cohort (including in the present study), and elsewhere (18, 19, 31, 47). In order to confirm these relationships and inform appropriate prescription opioid-related overdose prevention and response strategies, future research efforts should examine patterns of co-occurring drug use and risk behaviors associated with prescription opioid use in this setting.

Prescription opioids are unique from traditionally used illicit drugs in that they are consistent in their purity and dosage, raising the question about whether IDU who use these drugs non-medically are at a reduced risk for overdose due to an ability to better monitor their dosing. Our data do not support this hypothesis, as any stability in drug dosing is likely countered by high-intensity drug use. Drug market trends may also play a role in shaping this hypothesized lower overdose risk, as drug availability and costs likely facilitate transitions between prescription opioids and heroin, regardless of preference for one drug over the other.

We also found that daily heroin injection, recent incarceration, requiring help injecting, and injecting in public were all significantly and positively associated with non-fatal overdose within our sample. These findings are consistent with the results of previous studies (18, 19, 37, 47–49), and exemplify the severity of some of the many social and behavioral circumstances that individuals within this highly marginalized community frequently face.

We note several limitations to our study. VIDUS and ACCESS are not random samples, and our results may not be generalizable to other IDU populations. The self-reported nature of overdose may introduce the possibility of a bias; however, we feel that using this broad definition is advantageous in our setting, where poly-drug use is the norm and overdoses involving non-opioid substances are common. While we were able to analyze information over many years, each data point refers to events within the previous six months, thus limiting the ability to detect temporality between independent and outcome variables at each collection time. Further, since we did not have CES-D measures for the entire study period, we were only able to consider baseline depression as an independent variable in our

analyses. Therefore we were unable to assess how changes in depression over time may have affected our outcome of interest. Finally, we were unable to include the specific type or dose of prescription opioid(s) used by individuals, as this information was not available in earlier versions of our questionnaire. Future research should explore specific type, dose, and route of administration of prescription opioids in relation to non-fatal overdose.

In conclusion, our study demonstrates a relatively high rate of non-fatal overdose among IDU in Vancouver, which was independently associated with prescription opioid use after adjustment for other factors associated with non-fatal overdose including frequent heroin injection, recent incarceration, requiring help injecting and injecting in public. The emergence of prescription opioid use as a risk factor for non-fatal overdose highlights the potential to reduce overdose risk by tailoring interventions (e.g., take home naloxone) to this population, and highlights the need to better characterize the broader risk environment that influences risk of overdose for people who use prescription opioids.

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Table 1

Baseline bivariable summary of factors associated with non-fatal overdose among IDU in Vancouver, Canada, n = 1614

Non-fatal Overdose	Yes 118 (7.3%)	No 1496 (92.7%)	Odds Ratio (95% CI [*])	p - value
Prescription Opioid Use[†]				
Yes	55 (46.6)	471 (31.5)	1.90 (1.30 – 2.77)	0.001
No	63 (53.4)	1025 (68.5)		
Age[‡]				
Median (IQR [§])	38.6 (33.8 – 45.4)	41.8 (35.3 – 47.6)	-	0.044
Years Injecting[‡]				
Median (IQR)	18.5 (12.2 – 28.0)	19.2 (11.4 – 28.3)	-	0.841
Gender				
Male	74 (62.7)	999 (66.8)	0.84 (0.57 – 1.23)	0.368
Female	44 (37.3)	497 (33.2)		
Ethnicity				
Caucasian	82 (69.5)	906 (60.6)	1.53 (1.01 – 2.30)	0.042
Other	35 (29.7)	590 (39.4)		
Unstable Housing[†]				
Yes	89 (75.4)	1045 (69.9)	1.36 (0.88 – 2.11)	0.169
No	28 (23.7)	447 (29.9)		
Sex Work[†]				
Yes	22 (18.6)	225 (15.0)	1.33 (0.82 – 2.16)	0.253
No	93 (78.8)	1262 (84.4)		
Cocaine Injection[†]				
Daily	21 (17.8)	150 (10.0)	1.94 (1.18 – 3.20)	0.008
<Daily	97 (82.2)	1345 (89.9)		
Heroin Injection[†]				
Daily	54 (45.8)	409 (27.3)	2.24 (1.53 – 3.28)	<0.001
<Daily	64 (54.2)	1087 (72.7)		
Crack Smoking[†]				
Daily	63 (53.4)	609 (40.7)	1.67 (1.15 – 2.43)	0.007
<Daily	55 (46.6)	887 (59.3)		
Require Help Injecting[†]				
Yes	45 (38.1)	343 (22.9)	2.04 (1.38 – 3.01)	<0.001
No	72 (61.0)	1118 (74.7)		
Binge Drug Use[†]				
Yes	61 (51.7)	591 (39.5)	1.64 (1.13 – 2.39)	0.009
No	57 (48.3)	905 (60.5)		
Incarceration[†]				
Yes	37 (31.4)	255 (17.1)	2.24 (1.48 – 3.39)	<0.001

Non-fatal Overdose	Yes 118 (7.3%)	No 1496 (92.7%)	Odds Ratio (95% CI)*	p - value
No	80 (67.8)	1236 (82.6)		
Addiction Treatment[†]				
Yes	65 (55.1)	772 (51.6)	1.21 (0.82 – 1.77)	0.330
No	50 (42.4)	718 (48.0)		
HIV Serostatus				
Positive	38 (32.2)	550 (36.8)	0.82 (0.55 – 1.22)	0.322
Negative	80 (67.8)	946 (63.2)		
Benzodiazepine Use[‡]				
Yes	4 (3.4)	23 (1.5)	2.25 (0.76 – 6.61)	0.129 [£]
No	114 (96.6)	1473 (98.5)		
Heavy Alcohol Use[‡]				
Yes	22 (18.6)	233 (15.6)	1.24 (0.77 – 2.02)	0.379
No	96 (81.4)	1263 (84.4)		
Denied Treatment[‡]				
Yes	12 (10.2)	75 (5.0)	2.20 (1.16 – 4.17)	0.014
No	103 (87.3)	1415 (94.6)		
Injecting in Public[‡]				
Yes	75 (63.6)	552 (36.9)	2.97 (2.01 – 4.39)	<0.001
No	43 (36.4)	941 (62.9)		
Depression				
Yes	89 (75.4)	977 (65.3)	1.63 (1.06 – 2.51)	0.026
No	29 (24.6)	519 (34.7)		

* 95% CI = 95% Confidence interval

[†] Denotes events in the previous six months

[‡] Wilcoxon rank sum test was used for continuous variables

[§] IQR = Interquartile range

[£] p - value was from Fisher's Exact Test

Note: Not all cells add up to 1,614 as participants may choose not to answer sensitive questions

Table 2

Bivariable and multivariable GEE* of factors associated with non-fatal overdose among IDU in Vancouver, Canada, May 2005 – December 2013, n = 1614

Non-fatal Overdose	Unadjusted		Adjusted	
	Odds Ratio (95% CI) [†]	p - value	Odds Ratio (95% CI)	p - value
Prescription Opioid Use[‡]				
(yes vs. no)	2.03 (1.69 – 2.45)	<0.001	1.61 (1.32 – 1.95)	<0.001
Age				
(per year older)	0.98 (0.97 – 1.00)	0.020	-	-
Years Injecting				
(per year longer)	1.00 (0.99 – 1.01)	0.662	-	-
Gender				
(male vs. female)	0.98 (0.77 – 1.23)	0.834	-	-
Ethnicity				
(Caucasian vs. other)	1.18 (0.93 – 1.49)	0.183	-	-
Unstable Housing[‡]				
(yes vs. no)	1.18 (0.94 – 1.47)	0.158	-	-
Sex Work[‡]				
(yes vs. no)	1.09 (0.83 – 1.45)	0.522	-	-
Cocaine Injection[‡]				
(daily vs. <daily)	1.47 (1.13 – 1.91)	0.005	-	-
Heroin Injection[‡]				
(daily vs. <daily)	1.96 (1.59 – 2.41)	<0.001	1.38 (1.10 – 1.73)	0.005
Crack Smoking[‡]				
(daily vs. <daily)	1.27 (1.04 – 1.55)	0.021	-	-
Require Help Injecting[‡]				
(yes vs. no)	1.85 (1.50 – 2.29)	<0.001	1.55 (1.23 – 1.94)	<0.001
Binge Drug Use[‡]				
(yes vs. no)	1.41 (1.18 – 1.68)	<0.001	-	-
Incarceration[‡]				
(yes vs. no)	2.40 (1.93 – 2.97)	<0.001	1.88 (1.52 – 2.33)	<0.001
Addiction Treatment[‡]				
(yes vs. no)	1.02 (0.83 – 1.24)	0.884	-	-
HIV Serostatus				
(positive vs. negative)	0.91 (0.71 – 1.15)	0.413	-	-
Benzodiazepine Use[‡]				
(yes vs. no)	1.24 (0.66 – 2.33)	0.507	-	-
Heavy Alcohol Use[‡]				
(yes vs. no)	1.30 (1.04 – 1.62)	0.019	-	-
Denied Treatment[‡]				

	Unadjusted		Adjusted	
	Odds Ratio (95% CI) [†]	<i>p</i> - value	Odds Ratio (95% CI)	<i>p</i> - value
Non-fatal Overdose				
(yes vs. no)	1.59 (1.16 – 2.18)	0.004	-	-
Injecting in Public[‡]				
(yes vs. no)	2.27 (1.86 – 2.77)	<0.001	1.64 (1.32 – 2.04)	<0.001
Depression				
(yes vs. no)	1.95 (1.49 – 2.54)	<0.001	-	-

* GEE = Generalized estimating equation

[†] 95% CI = 95% Confidence interval

[‡] Denotes events in the previous six months