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Investigating A Bidirectional Relationship Between Overdose and Provision of Injection Initiation Assistance Among Persons Who Inject Drugs in Vancouver, Canada and Tijuana, Mexico

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Abstract

Background: Injection drug use is often initiated by assistance from an injection-knowledgeable peer. Persons who assist peers in injection initiation events often inject frequently, which heightens overdose risk. As such, overdose and injection initiation events may be correlated. To explore a potential relationship, we assessed temporal associations between experiencing a non-fatal

Ethics Approval

All participants reviewed the informed consent document and agreed to participate prior to enrollment. All study sites received ethical approval from their local institutional review boards: the University of British Columbia-Providence Health Care Research Ethics Board and la Universidad Xochicalco, Facultad de Medicina, Campus Tijuana Institutional Review Board.

In regards to article: “Investigating A Bidirectional Relationship Between Overdose and Injection Initiation Assistance Among Persons Who Inject Drugs in Vancouver, Canada and Tijuana, Mexico,” we, the authors, state: “Declarations of interest: none.”

overdose and assisting others in initiating injection drug use among persons who inject drugs in two North American cities – Vancouver, Canada and Tijuana, Mexico.

Methods: From 2014–2018, this retrospective cohort study included people who inject drugs from Vancouver (n=1332) and Tijuana (n=666) who completed a baseline and six-month follow-up interview. Within each site, we assessed bidirectional temporal associations using two separate multivariable logistic regression models: for model 1, recent provision of injection initiation assistance (at six months) was the outcome and recent overdose (at baseline) was the exposure; whereas; model 2, recent overdose (at six months) was the outcome and recent provision of injection initiation assistance (at baseline) was the exposure. Both models adjusted for potential confounders.

Results: Vancouver-based participants reporting overdose at baseline had 163% greater odds of reporting injection initiation assistance at followup (adjusted Odds Ratio [aOR] 2.63; 95% Confidence Interval [CI] 1.41–4.90); while participants reporting injection initiation assistance at baseline had 89% greater odds of reporting a non-fatal overdose at followup (aOR 1.89; 95% CI 1.00–3.57). Our Tijuana-based results did not conclude any associations.

Conclusion: Findings in Vancouver suggest that injection initiation assistance and overdose are a bidirectionally-associated phenomena. The present findings highlight the need for interventions that ensure that persons who provide injection initiation assistance are given overdose prevention support, both for themselves and for those they assist to initiate injection drug use. While our Tijuana-based results did not suggest a bidirectional relationship, preventative approaches should nonetheless be undertaken.

Keywords

Overdose; Opioids; Injection Drug Use; Injection Initiation

Introduction

In North America, fatal opioid overdoses remain a growing driver of mortality. Overdoses are driven by fluctuating street drug potency, leading to unknown drug and dose administration prior to consumption; this situation is exacerbated by the criminalization of drug use, which contributes to an environment in which people who use drugs are more vulnerable to drug-related harms and less access life-saving services.[1–5] A risk factor for opioid overdose is drug consumption via intravenous injection.[6,7] Injecting increases drug bioavailability by bypassing first-pass (or presystemic) metabolism, resulting in more potent and rapidly delivered drug effects.[8] In North America, an estimated 2.6 million people who inject drugs,[9] among whom 45% (>1 million) have experienced a non-fatal overdose.[10] Given the efficiency of injection as a route of drug administration, some who use drugs may be motivated to initiate injection drug use.[11,12]

The vast majority of injection initiation events involve an injection-naive individual seeking and receiving assistance from an injection-knowledgeable peer,[13–18] who are often frequent drug injectors[19] and subsequently at high risk of overdose. As such, there is concern that overdose and injection initiation events may be linked. In an effort to examine this potential phenomena, we assessed temporal associations, in both directions, between experiencing a

non-fatal overdose and assisting others in initiating injection drug use among people who inject drugs in two North American cities disproportionately impacted by drug injecting: Vancouver, Canada and Tijuana, Mexico.

Methods

Study settings, design and data sources

The study settings were chosen based on high incidence of injection initiation assistance, with one [Vancouver] already in the grips of a catastrophic fatal overdose crisis,[20,21] and the other [Tijuana, Mexico] demonstrating characteristics suggesting a plausible, eminent fatal overdose crisis.[22,23] Moreover, these settings have drastically different drug policies that shape access to harm reduction and treatment services.[22–28] We conducted a retrospective analysis of cohort data from people who inject drugs from Vancouver, Canada and Tijuana, Mexico involved in the PReventing Injecting by Modifying Existing Responses (PRIMER) study between 2014 and 2018. The PRIMER study is an international, multi-cohort consortium seeking to identify socio-structural factors that shape the provision of injection initiation assistance.[18] All PRIMER* participants are enrolled in one of four linked cohort studies detailed in the study abbreviation list.

Recruitment in both settings involved a mix of strategies including street-based engagement, flyers at harm reduction and shelter venues, and chain referrals from participants. Following informed consent, participants completed interviewer-administered questionnaires at baseline and semi-annually thereafter. Each questionnaire contained common items that capture participant sociodemographic information, drug use characteristics, and other drug-related behaviors (e.g., injecting practices). In 2014, cohort questionnaires were revised under the broader PRIMER study protocol to add items soliciting participants' experiences with providing injection initiation assistance.[18] We restricted our study to cohort participants who: 1) completed their PRIMER baseline interview (hereafter referred to as 'baseline'); 2) reported injection drug use pre-baseline; 3) completed six-month follow-up interview after baseline.

Measures

At baseline and six-month follow-up interviews, participants were asked whether they experienced a recent (non-fatal) overdose ("in the last six months, have you overdosed?") and whether they recently provided injection initiation assistance ("in the last six months, have you helped anybody inject who had never injected before?"). Those who answered yes to either question at either point-in-time are the focus of this study. The motivation for including repeated measures was to enable estimation of temporal associations between recent overdose and recent provision of injection initiation assistance bidirectionally. Additionally, we also identified *a priori* a set of baseline, self-reported covariates deemed to be potential confounders of the relationship between recent overdose and recent provision of injection initiation assistance based on existing evidence.[16,18,21,29,30] These included: age; sex; recent homelessness; drug injection frequency;[7,31] and non-injection drug use frequency.[32] All covariates qualified as 'recent' capture behaviours [<6 months].

Statistical analysis

To bidirectionally assess temporal associations between recent overdose and recent injection initiation assistance, we fit two multivariable logistic regression models per site: for the first model, we regressed recent injection initiation assistance (as outcome; assessed at six months) on recent overdose (as exposure; assessed at baseline); whereas, for the second model, we regressed recent overdose (as outcome; assessed at six months) on recent injection initiation assistance (as exposure; assessed at baseline). In both models, we purposefully specified an exposure measure that preceded the corresponding outcome measure by six months to establish temporality.[33] Resulting estimates of temporal associations between recent overdose and recent provision of injection initiation assistance are expressed as covariate-adjusted odds ratios with 95% confidence intervals (CI). For comparison with the covariate-adjusted estimates from regression analyses, we also produced unadjusted estimates of the temporal associations of interest using simple cross-tabulations. Analyses were restricted to complete cases. All analyses were performed in R (version 3.6.1).

Results

Baseline characteristics

Table 1 summarizes baseline characteristics among the 1332 and 666 eligible participants identified within Vancouver and Tijuana, respectively. Overall, participants in Vancouver were predominantly male (62.7%) and living in the Downtown Eastside (51.1%) neighborhood. The median age reported at baseline was 46.0 (interquartile range [IQR], 34.0–54.0), with half of participants reporting that their first injection occurred at least 22 years ago (IQR, 11.0, 32.0). For participants in Tijuana, the median age was 40.1 (IQR, 34.3–47.1), with the majority being male (59.3%). Similarly to Vancouver, half of participants reported that over 19.4 years had elapsed since their first injection (median, 19.4; IQR, 12.5, 26.7). At baseline, 11.3% of Vancouver participants and 4.5% of Tijuana participants reported a recent overdose; whereas, 4.7% of Vancouver participants and 5.6% of Tijuana participants reported recently providing injection initiation assistance at baseline.

Unadjusted and adjusted temporal associations between recent overdose and recent provision of injection initiation assistance

Table 2 presents cross-tabulations comparing the crude (or unadjusted) distributions of recent overdose and recent provision of injection initiation assistance within each site. Missing responses for both measures at six-months were infrequent in Vancouver (n=8 for recent provision of injection initiation assistance and n=2 for recent overdose), with no missing responses for either measure in Tijuana. The number (and proportion) of participants in Vancouver reporting recent provision of injection initiation assistance (57/1320 or 4.3%) and recent overdose (143/1305 or 11.0%) at six-months was higher than in Tijuana (24/666 or 3.6% and 27/666 or 4.1%, respectively). In Vancouver, recent overdose at baseline was associated with 462% greater odds of providing injection initiation assistance over 6-month follow-up (odds ratio [OR], 5.62; 95% confidence interval [CI], 3.20 to 9.88); while recent provision of injection initiation assistance at baseline was associated with 99% greater odds of a non-fatal overdose over 6-month follow-up (OR,

1.99; 95% CI 2.30 to 7.25). In Tijuana, the same temporal associations were estimated to be weaker in magnitude with noticeably wider corresponding 95% CI.

Table 3 summarizes the results of multivariable logistic regression analyses by site, which adjusted for age, sex, recent homelessness, recent frequency of IDU, and recent frequency of non-injection drug use - in estimating the temporal associations of interest. Among Vancouver participants, we found that those with a recent overdose at baseline had a significantly greater odds of providing injection initiation assistance to a peer in the following six months (adjusted OR [aOR], 2.63; 95% Confidence Interval [CI], 1.41 to 4.90); conversely, based on 1304 Vancouver-based participants, those who provided injection initiation assistance within the six months prior to baseline had a significantly greater odds of experiencing a non-fatal overdose in the next six months (aOR, 1.89; 95% CI, 1.00 to 3.57). In contrast, in Tijuana there was an absence of evidence based to suggest an association in either direction.

Relationship and rationale for providing injection initiation

We conducted an exploratory subanalysis of participants who provided injection initiation assistance within the six-month follow-up period by site (Supplemental Table 1). In both Vancouver and Tijuana, the most common reason for providing injection assistance was that the person seeking assistance "didn't know how to inject" (89.1% and 79.2%, respectively).

Discussion

In this study, we found evidence of a bidirectional relationship between experiencing a recent non-fatal overdose and providing injection initiation assistance among Vancouver-based participants who inject drugs, but not those in Tijuana.

Providing injection initiation assistance can place those who inject drugs in a position previously characterized as 'moral ambivalence,'[34] as injection is associated with pleasure but also with overdose, bloodborne infections, and other serious health issues.[35,36] For some, there is a moral code against injection initiation assistance;[35] whereas for others there is a moral imperative to share injection skills that reduce harm.[34,37–39,40] In the present study, those who experienced an overdose prior to baseline were significantly more likely to provide injection initiation assistance in the following six months. Our subanalysis showcased that the main motivation to assist in injection initiation was because a person didn't know how to inject. It is therefore plausible that those who overdosed prior to baseline were motivated by that experience to share harm-reducing (e.g. overdose) injection skills. Further research on injection initiation assistance intended to prevent overdose is warranted.

The present study also revealed a temporal relationship between providing injection initiation assistance and overdosing in the following six months. Importantly, all overdoses reported in this study were non-fatal. This could be explained by an overdose being attended by harm reduction staff, emergency services, or by peers possessing overdose education and naloxone distribution [OEND] training.[41–46] As such, supporting those who assist in injection initiation via a safer-injection "train-the-trainer" approach, coupled with OEND,[41,42,47,48] is suggested. However, non-fatal overdose can be a precursor for fatal

overdose, especially when consuming drugs alone.[30,49,50] As such, overdose-preventing interventions, like supervised consumption services [SCSs],[19,51,52] ought to be ramped up. SCSs also reduce interest in injection initiation due to less exposure to injection events.[53] Overall, overdose and injection initiation assistance are more common among those experiencing barriers to accessing SCSs, opioid agonist treatment [OAT][54] & safer opioid supply [SOS] programs;[55–58] and experiencing homelessness, cycles of incarceration,[17] and stigma,[59] which are likely roots of such barriers.[60] Therefore, efforts to reduce the incidence of injection initiation and overdose should focus on clinical and structural approaches such as SCSs, OAT & SOS, housing, and drug decriminalization.[16,53,61,62]

In Tijuana, a significant association between overdose and injection initiation assistance was not detected. Tijuana has lower rates of opioid overdose fatalities compared to Vancouver and other North American settings, though this may be related to underreporting.[23] Notably, drug using networks in Tijuana face high levels of instability[22] due to disbanding of encampments for unhoused persons and other harmful policing encounters leading to concealing drug use, a risk factor for overdose death.[44,49] Although overdose was not significantly correlated with injection initiation assistance, well-funded harm reduction programs could reduce the existing burden of injection-related infectious disease[63] and possibly prevent an imminent overdose crisis.[23]

This study has limitations typical of observational research involving people who use drugs. First, because drug-related behaviors like the provision of injection drug use initiation assistance is a highly stigmatized behavior,[38] it might have been underreported. However, we know of no reason why individuals who provide such assistance would have reported it differentially based on whether or not they experienced an overdose; however, non-differential misclassification of dichotomous measures tend, on average, to attenuate associations, suggesting a potential bias towards the null. Second, the data are generated from convenience samples in both Tijuana and Vancouver, and we cannot infer generalizability to the broader populations in either city. However, samples in both sites include highly marginalized individuals, and the data presented herein provide insight into the extreme vulnerabilities of criminalized populations in these settings.

Conclusion

In sum, the present findings contribute to the working knowledge that harm reduction interventions are key to preventing adverse outcomes associated with drug use. In Vancouver, we found evidence of a bidirectional relationship between overdose and injection initiation assistance. While this association was not observed in Tijuana, prevention via interventions in both cities – such as enhanced and supported supervised drug consumption sites and overdose prevention support for those comfortable with the provision of injection drug use initiation – may promote the wellbeing of people who use and inject drugs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Additional Abbreviations

OEND	Overdose Education and Naloxone Distribution
SCS	Supervised Consumption Service
OAT	Opioid Agonist Treatment
SOS	Safer Opioid Supply

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*Abbreviation List

PReventing Injecting by Modifying Existing Responses [PRIMER] Linked Cohort Studies and Inclusion Criteria[18]

Cohort Study*	Setting	Inclusion Criteria	Sample size [n]
Vancouver Injection Drug Users Study [VIDUS]	Vancouver	Age 18 or older; HIV negative; injected any drug	n=664
AIDS Care Cohort to Evaluate Access to Survival Services [ACCESS]**	Vancouver	Age 18 or older, HIV positive, past 6-month illicit drug use other than cannabis	n=459
At-Risk Youth Study [ARYS]	Vancouver	Ages between 14 to 26, illicit drug use pre-baseline, homeless or in youth shelter	n=209
Proyecto el Cuete IV [ECIV]	Tijuana	Age 18 or older, drug injection pre-baseline, Spanish or English speaking, lived in Tijuana	n=666

*PRIMER was approved by research ethics boards at the University of British Columbia (Vancouver), el Colegio de la Frontera Norte (Tijuana), and the University of California San Diego Institutional Review Board (Tijuana and Vancouver).

**Note: participants in the ACCESS* study were HIV-positive, resulting in an overrepresentation of people living with HIV from the Vancouver cohort.[64]

Table 1.

Participant baseline characteristics stratified by site.

	Vancouver (N=1332)	Tijuana (N=666)
Baseline characteristics	**n (%[a])**	**n (%[a])**
Recent overdose[b]		
Yes	150 (11.3%)	30 (4.5%)
No	1178 (88.7%)	636 (95.5%)
Missing	4	-
Recent provision of injection initiation assistance[b]		
Yes	61 (4.7%)	37 (5.6%)
No	1246 (95.3%)	629 (95.4%)
Missing	25	-
Age, median [IQR]	46.0 (34.0, 54.0)	40.1 (34.3, 47.1)
Sex		
Female	497 (37.3%)	271 (40.7%)
Male	834 (62.7%)	395 (59.3%)
Missing	1	-
Marital status		
Married	190 (14.3%)	297 (44.7%)
Other	1141 (85.7%)	367 (55.3%)
Missing	1	1
Recent homelessness[b]		
Yes	293 (22.0%)	247 (37.1%)
No	1039 (78.0%)	419 (62.9%)
Years since 1st injection, median [IQR]	22.0 (11.0, 32.0)	19.4 (12.5, 26.7)
Missing	3	3
Recent frequency of IDU[b]		
None	477 (35.8%)	91 (13.7%)
Less than weekly	192 (14.4%)	12 (1.8%)
Less than daily	215 (16.1%)	27 (4.1%)
Daily	448 (33.6%)	536 (80.5%)
Recent injection of[b,c]:		
Heroin	557 (41.8%)	380 (57.1%)
Cocaine[d]	248 (18.6%)	15 (2.3%)
Methamphetamine	417 (31.3%)	105 (15.8%)
Prescription opioid	225 (16.9%)	1 (<0.1%)
Recent frequency of non-injection drug use[b]		
None	579 (43.5%)	378 (56.8%)
Less than weekly	261 (19.6%)	46 (6.9%)

Baseline characteristics		Vancouver (N=1332) n (%[a])	Tijuana (N=666) n (%[a])
	Less than daily	267 (20.1%)	93 (1.4%)
	Daily	225 (16.9%)	149 (22.4%)
Recent non-injection use of[b,c]:			
	Heroin	146 (11.0%)	61 (9.2%)
	Cocaine[d]	135 (10.1%)	29 (4.4%)
	Methamphetamine	324 (24.3%)	268 (40.2%)
	Prescription opioid	153 (11.5%)	9 (1.4%)

Notes: IDU = injection drug use; IQR = interquartile range.

[a] Column percentages calculated with missing responses (where observed) excluded from denominator. Due to rounding, the sum of column percentages may not equal 100%.

[b] In the past 6-months.

[c] Participants could select multiple options; thus, sum of column totals may exceed 100%.

[d] Powder or crack cocaine.

Table 2.

Unadjusted temporal associations between recent overdose and recent provision of injection initiation assistance among persons who inject drugs in Vancouver, Canada, and Tijuana, Mexico – stratified by timing of measures and site.

a)

Vancouver				Tijuana			
Recent overdose (baseline)	Recent provision of injection initiation assistance (6 months)			Recent overdose (baseline)	Recent provision of injection initiation assistance (6 months)		
	Yes	No	Total		Yes	No	Total
Yes	22	127	149	Yes	2	28	30
No	35	1136	1171	No	22	614	636
Total	57	1263	1320	Total	24	642	666
Crude OR = 5.62; 95% CI = 3.20 to 9.88				Crude OR = 1.99; 95% CI = 0.45 to 8.90			

b)

Vancouver				Tijuana			
Recent provision of injection initiation assistance (baseline)	Recent overdose (6 months)			Recent provision of injection initiation assistance (baseline)	Recent overdose (6 months)		
	Yes	No	Total		Yes	No	Total
Yes	19	42	61	Yes	1	36	37
No	124	1120	1244	No	26	603	629
Total	143	1162	1305	Total	27	639	666
Crude OR = 4.09; 95% CI = 2.30 to 7.25				Crude OR = 0.64; 95% CI = 0.09 to 4.88			

Notes: OR = odds ratio; CI = confidence interval.

Table 3.

Results of multivariable logistic regression analyses assessing temporal associations between recent overdose and recent provision of injection initiation assistance among persons who inject drugs in Vancouver, Canada and Tijuana, Mexico.

a) Outcome: Recent provision of injection initiation assistance at six-months follow-up.

	Vancouver (n=1319)		Tijuana (n=666)	
Baseline characteristics	**aOR**	**95% CI**	**aOR**	**95% CI**
Recent overdose, yes vs no	2.63	1.41 to 4.90	1.97	0.43 to 9.09
Age, 1-year increase	0.93	0.91 to 0.96	1.01	0.97 to 1.06
Sex, male vs female	1.54	0.86 to 2.79	1.44	0.57 to 3.60
Recent homelessness, yes vs no	0.55	0.29 to 1.07	1.01	0.43 to 2.39
Recent frequency of IDU				
Less than weekly vs none	3.41	0.97 to 12.1	NR	NR
Less than daily vs none	3.82	1.16 to 12.6	3.34	0.44 to 25.5
Daily vs none	5.28	1.80 to 15.5	1.53	0.35 to 6.78
Recent frequency of non-injection drug use				
Less than weekly vs none	1.55	0.67 to 3.58	1.50	0.32 to 7.03
Less than daily vs none	2.00	0.90 to 4.44	1.95	0.65 to 5.88
Daily vs none	2.12	0.96 to 4.68	1.47	0.51 to 4.26

b) Outcome: Recent overdose at six-months follow-up.

	Vancouver (n=1304)		Tijuana (n=666)	
Baseline characteristics	**aOR**	**95% CI**	**aOR**	**95% CI**
Recent provision of injection initiation assistance, yes vs no	1.89	1.00 to 3.57	0.50	0.06 to 3.91
Age, 1-year increase	0.97	0.95 to 0.98	0.95	0.91 to 1.00
Sex, male vs female	1.11	0.76 to 1.63	0.76	0.33 to 1.73
Recent homelessness, yes vs no	1.78	1.18 to 2.70	0.69	0.31 to 1.51
Recent frequency of IDU				
Less than weekly vs none	2.97	1.40 to 6.27	NR	NR
Less than daily vs none	5.11	2.59 to 10.1	NR	NR
Daily vs none	4.37	2.39 to 8.18	1.27	0.36 to 4.42
Recent frequency of non-injection drug use				
Less than weekly vs none	1.87	1.12 to 3.11	0.61	0.08 to 4.82
Less than daily vs none	1.39	0.82 to 2.37	0.82	0.22 to 2.99
Daily vs none	1.76	1.05 to 2.95	1.65	0.67 to 4.06

Notes: aOR = adjusted odds ratio (adjusted for all baseline characteristics presented in table); CI = confidence interval; IDU = injection drug use; NR = not reported (no observed events in group being compared to reference group).