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Initiation into prescription opioid injection and associated trends in heroin use among people who use illicit drugs

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Abstract

Objectives—Prescription opioid (PO) injection among people who use illicit drugs (PWUD) is an ongoing concern, yet little is known about drug use trajectories associated with initiating PO injection, including potential associations with heroin use. This study aimed to identify predictors of PO injection initiation among PWUD, and examine trends in heroin use before and after initiating PO injection.

Methods—Data were merged from three cohorts of PWUD recruited between September 2005 and November 2015. Predictors of PO injection initiation were identified using extended Cox regression models. Trends in heroin use pre- and post-initiation were examined with McNemar's test and compared to matched controls with linear growth curve models.

Results—Among 1580 participants, 247 initiated PO injection yielding an incidence density of 3.9 (95% Confidence Interval [CI]: 3.4–4.4) per 100 person-years. In a multivariable analysis, independent predictors of PO injection initiation included heroin injection (Adjusted Hazard Ratio [AHR] = 4.39, 95% CI: 3.24–5.95) and non-injection PO use (AHR=1.99, 95% CI: 1.25–3.17). In a sub-analysis, compared to matched controls, PO injection corresponded with elevated heroin use post-initiation ($p = 0.05$).

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Contributors: SL, TK, and KD designed the study, and SL drafted the original manuscript. KD is the Primary Investigator for the At-Risk Youth Study; KH and TK are the Primary Investigators for the Vancouver Injection Drug Users Study; M-JM is the Primary Investigator for the AIDS Care Cohort to evaluate Exposure to Survival Services. HD carried out all statistical analyses. All co-authors contributed to revisions of previous drafts of the manuscript, and approved the final draft.

Discussion—In this study, heroin use and non-injection PO use strongly predicted PO injection initiation. Those who initiated PO injecting had elevated heroin use patterns post-initiation compared to controls. These findings suggest that transitioning to PO injection does not appear to be a substitute for heroin use among PWUD. These findings highlight the importance of addressing PO injection in harm reduction and treatment settings.

Keywords

Prescription opioids; Heroin; Initiation; Injection drug use

1. Introduction

Prescription opioid (PO) use is a major public health concern across Canada and the United States (US), where both countries are responding to unprecedented rates of opioid dependence (Fischer et al., 2010; Rosenblum et al., 2007) and overdose (Centers for Disease Control and Prevention, 2012; Fischer et al., 2013). There is widespread concern that engaging in non-medical PO use facilitates transition into higher risk illicit drug use, including injection drug use (Cerde et al., 2015; Jones, 2013; Novak et al., 2015; Pollini et al., 2011). Using POs by injection is relatively common among people who inject drugs (Bruneau et al., 2012; Horyniak et al., 2015; Lake et al., 2015), and has been linked with various negative health outcomes, including Hepatitis C (HCV) infection (Bruneau et al., 2012; Havens et al., 2013), and non-fatal overdose (Havens et al., 2011; Lake et al., 2015; Silva et al., 2013). However, little is known about transitions into PO injection among those who are already engaged in risky illicit drug use scenes where heroin is readily available and commonly used. Specifically, factors within the risk environment (Rhodes, 2002) that may shape transitions into PO injecting have not been fully explored. The risk environment refers to a host of macro- and micro-level physical, social, economic, and policy exposures that marginalized populations, including people who use illicit drugs, may be subjected to within their daily lives (Rhodes, 2002). In theory, these structural exposures (e.g., incarceration, homelessness) interact within one's lived environment to exacerbate vulnerability to various harms including risky drug use patterns and drug-related morbidity/mortality (Rhodes, 2009).

Understanding drug use trajectories that coincide with PO injection initiation may help inform appropriate prevention and response strategies. Whereas non-medical PO use is known to increase the odds of riskier drug use, including heroin use, in young, nationally-representative samples (Cerde et al., 2015; Palamar et al., 2016), the impacts of PO injection initiation on patterns of heroin use are not well characterized within poly-drug using communities. The consistent dosage and purity of POs may create the perception that POs are comparatively safer than drugs manufactured illicitly, including heroin (Firestone and Fischer, 2008). This perception could be particularly pronounced in settings where heroin quality is unpredictable, or where other high potency opioids (e.g., fentanyl) are commonly added to heroin, and thereby contribute to elevated overdose rates (Algren et al., 2013). It is possible that within populations of people who use illicit drugs (PWUD), PO injection may actually be linked with decreasing heroin use.

We, therefore, sought to both examine predictors of initiation into PO injection among a group of PWUD, and explore the patterns of heroin use before and after PO injection initiation.

2. Materials and methods

2.1. Study sample

Data for this study was derived from three ongoing prospective cohorts of people who use illicit drugs in Vancouver: the Vancouver Injection Drug Users Study (VIDUS), the AIDS Care Cohort to evaluate Exposure to Survival Services (ACCESS), and the At-Risk Youth Study (ARYS). All three cohorts have been described in detail previously (Milloy et al., 2015; Strathdee et al., 1997; Wood et al., 2006). Briefly, VIDUS, which began recruitment in 1996, follows HIV-negative adults who use injection drugs and ACCESS, which began recruitment in 2005, follows HIV-positive adults who use illicit drugs, while ARYS, which began recruitment in 2005, follows street-involved youth and young adults who use illicit drugs. To be eligible for inclusion, VIDUS participants must report injecting a drug in the month prior to enrolment, while ACCESS and ARYS participants must report using an illicit drug (other than cannabis) in the month prior to enrolment. Study participants are recruited on an ongoing basis through self-referral, street outreach, and snow-ball sampling in various areas of downtown Vancouver including the Downtown Eastside (DTES): a geographically small, highly concentrated urban neighbourhood with an open illicit drug use scene and high rates of HIV/AIDS and homelessness (Linden et al., 2013).

At baseline and bi-annually, participants in all studies complete an interviewer-administered questionnaire eliciting time-updated socio-demographic, behavioural, and health-related information. Study nurses collect blood samples for HIV/HCV antibody testing or clinical HIV monitoring and provide basic referrals to appropriate health care services if needed. Participants receive a \$30 (CAD) honorarium upon completion of each study visit. All study instruments and follow-up procedures are harmonized to facilitate combined data analysis. The University of British Columbia/Providence Health Care Research Ethics Board provided ethical approval for these studies.

2.2. Measures

The present study was restricted to participants who completed a baseline and at least one follow-up questionnaire between September 2005 and November 2014. In order to capture participants who had initiated PO injection, the study was further restricted to participants who were naïve to PO injection (i.e., had no previous lifetime history of PO injection) at baseline. To capture the outcome of interest, we asked study participants at each interview to indicate which, if any, POs they had injected in the previous six months. The list of POs provided to study participants underwent annual modifications to reflect current trends in PO availability and use: the most recent questionnaire included options for OxyNeo, OxyContin, and Percocet (i.e., oxycodone); Tylenol3 (i.e., codeine); morphine; Dilaudid (i.e., hydromorphone); Demerol (i.e., meperidine); methadone; fentanyl; Vicodin (i.e., hydrocodone); and Talwin (i.e., pentazocine). Participants could also specify any POs they

used that were not on the list. Initiation into PO injection was determined from the follow-up period corresponding with the first report of PO injection.

We included several demographic, socio-structural, and behavioural factors hypothesized to contribute to the risk environment and to be potentially associated with initiation into PO injection. Demographic factors included: gender (female vs. male); age (per year older); ethnicity (Caucasian vs. non-Caucasian); and highest completed level of formal education (secondary vs. <secondary). Social and environmental factors included: self-reported area of residence (Downtown Eastside vs. other); drug or alcohol addiction treatment (non-methadone treatment, methadone treatment, or both methadone and non-methadone treatments vs. no treatment); homelessness; incarceration; drug dealing; and sex work (all yes vs. no). Drug use and related behavioural factors included: 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, according to the National Institutes on Alcohol Abuse and Alcoholism (National Institute on Alcohol Abuse and Alcoholism)]; heroin injection; heroin non-injection; cocaine injection; cocaine/crack non-injection; methamphetamine injection; methamphetamine non-injection; PO non-injection; and any marijuana use (all yes vs. no). All socio-environmental and drug use/behavioural variables are time-updated and refer to events in the 6-month period prior to the interview. Finally, we considered adverse life events that may increase susceptibility to initiating PO injection, including childhood sexual abuse (measured with the Childhood Trauma Questionnaire [CTQ]; moderate-severe vs. mild-none), and suicide attempt in the previous six months (yes vs. no). We also included the follow-up period (i.e., 6-month interview intervals beginning with September 2005–January 2006) and study cohort (reference: ARYS) to control for potential influences of calendar time and cohort membership, respectively. In order to confirm that the explanatory variables preceded initiation of PO injection, all time-updated measures were lagged to the study interview prior to the outcome assessment.

2.3. Analysis

First, we used Pearson's Chi-Square and Wilcoxon rank sum tests to examine the baseline characteristics of the sample, stratified by the outcome of interest. Bivariable and multivariable extended Cox regression models were used to determine the relative hazard of PO injection initiation associated with each independent variable. The inclusion of time-updated covariates in an extended Cox model negates the requirement of the proportional hazards assumption (Kleinbaum and Klein, 1996). Variables that were associated with the outcome at $p < 0.10$ in the bivariable model were included into an exploratory multivariable model. Using a stepwise backward approach, covariates were removed one-by-one beginning with the covariate with the highest p -value. Akaike information criterion (AIC) was examined at each step. The final model was selected based on lowest AIC. Justification for this approach has been detailed in previous studies (Lima et al., 2008; Marshall et al., 2011).

We designed a sub-analysis to compare the proportion of participants who reported heroin use before and after the period of PO injection initiation. To control for changing drug use patterns within the cohorts over time, we matched each case of PO injection initiation with

four participants who did not initiate PO injecting over the same calendar period (indicated by the variable “follow-up period”). Thus, only participants with three or more follow-ups were eligible for this sub-analysis. Within each group (PO initiators and controls), McNemar's test was used to compare the proportion of participants reporting selected recent (i.e., previous six months) heroin use patterns (any heroin injection, daily heroin injection, any heroin non-injection, daily non-injection) in a period before vs. after the initiation period. For this analysis, “before” and “after” refer to the most recent 6-month follow-up periods before and after the corresponding period of PO injection initiation, respectively. In order to determine whether changes in heroin use over time in the PO injection initiation group were statistically different than the control group, we built linear growth curve models for each heroin use variable, adjusted for all baseline covariates that differed between cases and controls at $p < 0.05$. Age, gender, and ethnicity were included regardless of significance level. In these models, the slope represents the change in heroin use pattern by group (i.e., initiator vs. control) over time (before vs. after) and the p -value corresponds to the significance of the interaction term. This method has been employed in previous studies to compare before-after trends in drug use or drug using behaviours between initiators and non-initiators of some event (DeBeck et al., 2009; Rachlis et al., 2010; Vlahov et al., 2001). All tests of significance were two-sided. All statistical analyses were performed using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA).

3. Results

Between September 2005 and November 2014, 1920 participants were naïve to PO injection at baseline. Of these, 1580 (82.3%) completed at least one follow-up interview and were eligible for this study, including 521 (33.0%) women. The excluded participants were more likely to be Caucasian (65.9% vs. 56.1%, $p < 0.001$) and to have a younger median age (22.4 vs. 32.2, $p < 0.001$), and differed according to certain baseline drug use characteristics including being less likely to have injected heroin at baseline (18.2% vs. 25.0%, $p = 0.008$), more likely to have used heroin by non-inject at baseline (20.6% vs. 14.0%, $p = 0.02$), and more likely to have used POs by non-injection at baseline (9.1% vs. 5.7%, $p = 0.016$). Together, the study sample contributed 11889 study observations over a median of 6 study visits per participant (Interquartile Range [IQR]: 3–11), and the median follow-up time was 42.1 months (IQR: 17.2–84.0). In total, 247 (15.6%) participants initiated PO injection over 6396.12 person-years of follow-up for an incidence rate of 3.9 (95% Confidence Interval [CI]: 3.4–4.4) per 100 person-years. A summary of the baseline study sample characteristics, stratified by any PO injection over the study period, is provided in Table 1.

Factors significantly and positively associated with PO injection initiation at $p < 0.05$ in the bivariable analysis included Caucasian ethnicity, ACCESS or VIDUS membership (vs. ARYS), methadone maintenance treatment (with or without non-methadone addiction treatment), drug dealing, heroin injection, cocaine injection, crack or cocaine non-injection, methamphetamine injection, and PO non-injection (Table 2). The study follow-up period was negatively associated with PO injection initiation such that the hazard of PO injection initiation decreased by approximately 4% for each additional 6-month interview interval (Table 2). In the adjusted analysis, factors that remained significantly and positively associated with initiating PO injection at $p < 0.05$ were: Caucasian ethnicity (Adjusted

Hazard Ratio [AHR]: 1.36, 95% CI: 1.04–1.79); high school completion (AHR: 1.44, 95% CI: 1.12–1.86); recent Downtown Eastside residency (AHR: 1.32, 95% CI: 1.01–1.72); recent addiction treatment enrolment (methadone only: AHR: 4.46, 95% CI: 2.03–9.80); both methadone and non-methadone: AHR: 2.45 (1.85–3.24); recent heroin injection (AHR: 4.47, 95% CI: 3.33–6.01); recent cocaine injection (AHR: 1.41, 95% CI: 1.07–1.86); recent methamphetamine injection (AHR: 1.70, 95% CI: 1.22–2.37); and recent PO non-injection use (AHR: 2.03, 95% CI: 1.28–3.20). Earlier follow-up period (i.e., earlier calendar date) was negatively associated with PO injection initiation (AHR: 0.96, 95% CI: 0.93–1.00).

In total, 1362 participants were eligible for the sub-analyses, which examined trends in heroin use before and after PO injection initiation. Of these, 218 (16.0%) were considered PO injection initiators, and were individually matched to 4 non-initiators randomly selected based on the initiation follow-up period. Remaining non-matched controls were removed for a total of 1090 participants in the analytic sub-sample ($n = 218$ “initiators”; $n = 872$ controls). The 490 participants who were excluded from this analysis due to limited follow-up ($n = 218$) and random non-selection as a control ($n = 272$) were compared to those retained in the sub-analyses on the basis of general demographic characteristic, and were found to have a younger median age (24.1 vs. 36.5, $p < 0.001$), but did not differ significantly with respect to gender and ethnicity. In terms of demographic characteristics, cases did not differ from controls on the basis of age or gender, but were more likely to be Caucasian (63.3% vs. 52.5%, $p = 0.004$) and to have obtained at least a high school education (51.8% vs. 41.4%, $p = 0.008$). Cases differed from controls according to other baseline behavioural characteristics including DTES residency (67.0% vs. 49.0%, $p < 0.001$); receiving some form of addiction treatment (55.0% vs. 37.4%, $p < 0.001$); drug dealing (43.1% vs. 30.6%, $p < 0.001$); heavy alcohol use (14.7% vs. 27.1%); any heroin injection (57.8% vs. 20.2%, $p < 0.001$); any heroin non-injection (16.5% vs. 10.9%, $p = 0.025$); cocaine injection (41.3% vs. 24.2%, $p < 0.001$); crack non-injection (82.1% vs. 73.7%, $p = 0.012$); methamphetamine injection (14.7% vs. 6.9%, $p < 0.001$); and VIDUS (51.8% vs. 40.1%) or ARYS (22.0% vs. 34.3%) cohort membership ($p = 0.001$).

Table 3 (top) presents the proportion of initiators and controls reporting selected heroin use behaviours in the periods before and after PO injection initiation, as well as the results of the McNemar's test to assess the significance of proportion changes within groups. Increases in the proportion of cases reporting both daily (28.4% to 35.3%, $p = 0.075$) and any heroin injection (61.9% to 68.4%, $p = 0.090$) from before to after the initiation event approached conventional significance, while the proportion of controls reporting heroin injection (daily and any) over this period remained stable. The proportion of any non-injection heroin use among controls decreased significantly (8.4% to 5.4%, $p = 0.002$), while remaining stable in the initiators. As shown in Table 3 (bottom), when entered into separate linear growth curve models adjusted for differences between cases and controls, the between-group changes were found to be significant for daily heroin injection ($p = 0.049$) and any heroin injection ($p = 0.011$), and moderately significant for any heroin non-injection ($p = 0.065$).

4. Discussion

In the present study, we sought to understand the factors associated with transitioning into PO injecting among individuals who are already entrenched in the illicit drug use scene at the time of initiation. To our knowledge, this is the first study to examine predictors of PO injection initiation, rather than PO use more generally. We found that Caucasian ethnicity, higher education, earlier follow-up period, Downtown Eastside residency, methadone treatment, heroin injection, cocaine injection, methamphetamine injection, and PO non-injection significantly predicted the event of initiating PO injection.

The finding that Caucasian ethnicity and higher education predicted PO injection has been demonstrated elsewhere (Pollini et al., 2011), and is in contrast to studies of other illicit drugs where these demographic factors have tended to protect against injection initiation (Werb et al., 2013). We also found that later study follow-up period was negatively associated with PO injection, which corresponds with a decreasing prevalence of PO injection previously observed in this setting (Lake et al., 2015). The Downtown East-side is Vancouver's epicenter for injection drug use, and our finding that residents of this neighbourhood were more likely to initiate PO injection is consistent with recent research of initiation into injection drug use (Chami et al., 2013) as well as a recent study of correlates of PO injection among people who inject drugs (PWID) in Montreal (Sacks-Davis et al., 2016). In the latter study, inner-city PWID had 1.5 times the odds of injecting POs compared to their counterparts who lived in less densely-populated surrounding areas (Sacks-Davis et al., 2016). This finding is particularly of importance, as inner-city residence was also shown to exacerbate the risk of HCV associated with PO injection (Sacks-Davis et al., 2016). Thus, future work among PWUD in Vancouver should examine whether predictors and outcomes of PO injection vary according to DTES residence. A surprising finding was that individuals on methadone maintenance treatment (either alone or over the same period as non-methadone addiction treatment) had an increased risk of PO injection initiation. A plausible explanation of this finding is that prescribed methadone is being injected by some of those enrolled on treatment; however, deconstruction of the outcome variable revealed only 18 (0.15%) observations of methadone injecting. Another potential interpretation of this finding is that addiction treatment could be serving as a marker for severity of addiction. Further investigation will be required to elucidate the underlying mechanisms driving this association. Our finding that non-injection PO use significantly predicted PO injection was expected in light of other studies observing this transition pathway among young (Lankenau et al., 2012b) and rural (Young and Havens, 2012) drug using populations. However, in this sample of experienced PWUD, other injection drug use, including heroin, cocaine, and methamphetamine injection, also significantly predicted transition to PO injection. While several studies involving nationally representative samples of the younger population have focused on the trend of transitioning from non-medical PO use to heroin initiation (Cerdeira et al., 2015; Jones, 2013; Lankenau et al., 2012b), our finding suggests a reverse trend may also exist among individuals who are regularly involved in or exposed to high-risk poly-drug use scenes. Furthermore, as our sample also consists of many long-term, older PWUD, this finding aligns with a clear cohort effect of heroin preceding POs in older drug users (Mars et al., 2014; Novak et al., 2015).

Further, in a sub-analysis, with the exception of daily non-injection heroin use, we found that heroin use patterns increased (any injection, daily injection) or persisted (any non-injection) following PO injection initiation; yet, over this same period, these patterns remained stable or decreased, respectively, in controls. Though qualitative research among PWUD has pointed to instances of POs being used to curb heroin use (Lankenau et al., 2012a), the current findings do not support this hypothesis among our population of PWUD, at least in terms of the first event of PO injection. In contrast, this analysis demonstrates that the event of initiating PO injection may actually mark an increase, rather than a decrease, in heroin use. It is likely that many PO initiators are heroin users that initiate PO injecting in parallel with increasing opioid dependence, perhaps due to better market availability of POs versus heroin at time of initiation - another common narrative emerging from qualitative work (Firestone and Fischer, 2008; Lankenau et al., 2012a). This finding is concerning in light of recent work in the current study setting demonstrating that, relative to those who inject non-opioid drugs, the odds of non-fatal overdose are increased by approximately 72% for those who inject heroin and 146% for those who inject both heroin and POs (Lake et al., 2015).

This study is subject to limitations. The three cohorts examined in these analyses do not constitute random samples and may not necessarily generalize to drug using populations in other settings. We note that participants who were excluded from the primary analysis due to only having completed a baseline interview differed according to ethnicity, age, heroin use, and PO non-injection at baseline. Participants excluded from sub-analyses due to having completed less than three interviews differed according to younger age. Second, we relied on self-reported drug use behaviours, which are susceptible to recall bias and socially desirable responses –particularly underreporting. However, we have no reason to suspect that any independent variables, including heroin injection, would be reported differentially according to PO injection initiation status. Third, there were certain potential predictors that we were not able to examine in the present analysis that could have impacted the results of this study. Specifically, we could not assess whether pain was a predictor of PO injection, as this variable was only recently added to the study questionnaire. Preliminary cross-sectional research with some members of our study population demonstrates that pain is common among PWUD, and undertreated pain may lead to seeking pain relief including POs and heroin from illicit sources (Voon et al., 2014, 2015). Finally, although controls were randomly selected, we were unable to achieve comparable groups with respect to all predictors of interest; however, we attempted to control for these differences statistically in the growth curve analyses.

The present analysis sheds light on PO injection initiation within a high intensity drug use scene where poly-drug use is the norm. People who inject POs are an important group for targeted harm reduction and treatment efforts in this setting, as those initiating PO injection tended to be experienced in other injection drug use and may engage in increased heroin use after the initiation event. Addiction treatment and harm reduction programs may be key settings for efforts aimed at preventing transitions into PO injection and promoting safer PO injecting. However, appropriate prevention strategies should be informed by future research that seeks to understand the nature of this under-explored association.

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References

- Algren DA, Monteilh CP, Punja M, Schier JG, Belson M, Hepler BR, Schmidt CJ, Miller CE, Patel M, Paulozzi LJ, Straetemans M, Rubin C. Fentanyl-associated fatalities among illicit drug users in Wayne county, michigan (July 2005–May 2006). *J Med Toxicol*. 2013; 9:106–115. [PubMed: 23359211]
- Bruneau J, Roy E, Arruda N, Zang G, Jutras-Aswad D. The rising prevalence of prescription opioid injection and its association with hepatitis C incidence among street-drug users. *Addiction*. 2012; 107:1318–1327. [PubMed: 22248184]
- Centers for Disease Control Prevention. Prescription drug overdoses – a U.S. epidemic. *MMWR*. 2012; 61:10–13. [PubMed: 22237030]
- Cerda M, Santaella J, Marshall BD, Kim JH, Martins SS. Nonmedical prescription opioid use in childhood and early adolescence predicts transitions to heroin use in young adulthood: a national study. *J Pediatr*. 2015; 167:605–612. e601–e602. [PubMed: 26054942]
- Chami G, Werb D, Feng C, DeBeck K, Kerr T, Wood E. Neighborhood of residence and risk of initiation into injection drug use among street-involved youth in a Canadian setting. *Drug Alcohol Depend*. 2013; 132:486–490. [PubMed: 23587537]
- DeBeck K, Kerr T, Li K, Milloy MJ, Montaner J, Wood E. Incarceration and drug use patterns among a cohort of injection drug users. *Addiction*. 2009; 104:69–76. [PubMed: 19133890]
- Firestone M, Fischer B. A qualitative exploration of prescription opioid injection among street-based drug users in Toronto: behaviours, preferences and drug availability. *Harm Reduct J*. 2008; 5:30. [PubMed: 18928556]
- Fischer B, Nakamura N, Rush B, Rehm J, Urbanoski K. Changes in and characteristics of admissions to treatment related to problematic prescription opioid use in Ontario, 2004–2009. *Drug Alcohol Depend*. 2010; 109:257–260. [PubMed: 20197216]
- Fischer B, Jones W, Rehm J. High correlations between levels of consumption and mortality related to strong prescription opioid analgesics in British Columbia and Ontario, 2005–2009. *Pharmacoepidemiol Drug Saf*. 2013; 22:438–442. [PubMed: 23319301]
- Havens JR, Oser CB, Knudsen HK, Lofwall M, Stoops WW, Walsh SL, Leukefeld CG, Kral AH. Individual and network factors associated with non-fatal overdose among rural Appalachian drug users. *Drug Alcohol Depend*. 2011; 115:107–112. [PubMed: 21126831]
- Havens JR, Lofwall MR, Frost SD, Oser CB, Leukefeld CG, Crosby RA. Individual and network factors associated with prevalent hepatitis C infection among rural Appalachian injection drug users. *Am J Public Health*. 2013; 103:e44–52.
- Horyniak D, Agius PA, Degenhardt L, Reddel S, Higgs P, Aitken C, Stooze M, Dietze P. Patterns of, and factors associated with, illicit pharmaceutical opioid analgesic use in a prospective cohort of people who inject drugs in Melbourne, Australia. *Subst Use Misuse*. 2015; 50:1650–1659. [PubMed: 26576630]

- Jones CM. Heroin use and heroin use risk behaviors among nonmedical users of prescription opioid pain relievers –United States, 2002–2004 and 2008–2010. *Drug Alcohol Depend.* 2013; 132:95–100. [PubMed: 23410617]
- Kleinbaum, DG.; Klein, M. *Survival Analysis.* Springer-Verlag; New York: 1996.
- Lake S, Hayashi K, Buxton J, Milloy MJ, Dong H, Montaner J, Wood E, Kerr T. The effect of prescription opioid injection on the risk of non-fatal overdose among people who inject drugs. *Drug Alcohol Depend.* 2015; 156:297–303. [PubMed: 26454837]
- Lankenau S, Teti M, Silva K, Bloom J, Harocopos A, Treese M. Patterns of prescription drug misuse among young injection drug users. *J Urban Health.* 2012a; 89:1004–1016. [PubMed: 22684424]
- Lankenau SE, Teti M, Silva K, Jackson Bloom J, Harocopos A, Treese M. Initiation into prescription opioid misuse amongst young injection drug users. *Int J Drug Policy.* 2012b; 23:37–44. [PubMed: 21689917]
- Lima VD, Harrigan R, Murray M, Moore DM, Wood E, Hogg RS, Montaner J. Differential impact of adherence on long-term treatment response among naive HIV-infected individuals. *AIDS.* 2008; 22:2371–2380. [PubMed: 18981777]
- Linden IA, Mar MY, Werker GR, Jang K, Krausz M. Research on a vulnerable neighborhood – the Vancouver downtown eastside from 2001 to 2011. *J Urban Health.* 2013; 90:559–573. [PubMed: 23161093]
- Mars SG, Bourgois P, Karandinos G, Montero F, Ciccarone D. Every ‘never’ I ever said came true: transitions from opioid pills to heroin injecting. *Int J Drug Policy.* 2014; 25:257–266. [PubMed: 24238956]
- Marshall BD, Wood E, Shoveller JA, Buxton JA, Montaner J, Kerr T. Individual, social, and environmental factors associated with initiating methamphetamine injection: implications for drug use and HIV prevention strategies. *Prev Sci.* 2011; 12:173–180. [PubMed: 21274628]
- Milloy MJ, Wood E, Kerr T, Hogg B, Guillemi S, Harrigan PR, Montaner J. Increased prevalence of controlled viremia and decreased rates of HIV drug resistance among HIV-positive people who use illicit drugs during a community-wide Treatment-as-Prevention initiative. *Clin Inf Dis.* 2015; 62:640–647.
- National Institute on Alcohol Abuse and Alcoholism Drinking Levels Defined. [accessed 01.09.15] <http://www.niaaa.nih.gov/alcohol-health/overview-alcohol-consumption/moderate-binge-drinking>
- Novak SP, Bluthenthal R, Wenger L, Chu D, Kral AH. Initiation of heroin and prescription opioid pain relievers by birth cohort. *Am J Public Health.* 2015; 106:298–300. [PubMed: 26691120]
- Palamar JJ, Shearston JA, Dawson EW, Mateu-Gelabert P, Ompad DC. Nonmedical opioid use and heroin use in a nationally representative sample of us high school seniors. *Drug Alcohol Depend.* 2016; 158:132–138. [PubMed: 26653341]
- Pollini RA, Banta-Green CJ, Cuevas-Mota J, Metzner M, Teshale E, Garfein RS. Problematic use of prescription-type opioids prior to heroin use among young heroin injectors. *Subst Abuse Rehabil.* 2011; 2:173–180. [PubMed: 23293547]
- Rachlis BS, Wood E, Li K, Hogg RS, Kerr T. Drug and HIV-related risk behaviors after geographic migration among a cohort of injection drug users. *AIDS Behav.* 2010; 14:854–861. [PubMed: 18427970]
- Rhodes T. The ‘risk environment’: a framework for understanding and reducing drug-related harm. *Int J Drug Policy.* 2002; 13:85–94.
- Rhodes T. Risk environments and drug harms: a social science for harm reduction approach. *Int J Drug Policy.* 2009; 20:193–201. [PubMed: 19147339]
- Rosenblum A, Parrino M, Schnoll SH, Fong C, Maxwell C, Cleland CM, Magura S, Haddox JD. Prescription opioid abuse among enrollees into methadone maintenance treatment. *Drug Alcohol Depend.* 2007; 90:64–71. [PubMed: 17386981]
- Sacks-Davis R, Daniel M, Roy E, Kestens Y, Zang G, Ramos Y, Hellard M, Jutras Aswad D, Bruneau J. The role of living context in prescription opioid injection and the associated risk of hepatitis C infection. *Addiction.* 2016 epub ahead of print.
- Silva K, Schrager SM, Kecojevic A, Lankenau SE. Factors associated with history of non-fatal overdose among young nonmedical users of prescription drugs. *Drug Alcohol Depend.* 2013; 128:104–110. [PubMed: 22974490]

- Strathdee SA, Patrick DM, Currie SL, Cornelisse PGA, Rekart ML, Montaner J, Schechter MT, O'Shaughnessy MV. Needle exchange is not enough: lessons from the Vancouver injecting drug use study. *AIDS*. 1997; 11:F59–F65. [PubMed: 9223727]
- Vlahov D, Safai M, Lai S, Strathdee SA, Johnson L, Sterling T, Celentano DD. Sexual and drug risk-related behaviours after initiating highly active antiretroviral therapy among injection drug users. *AIDS*. 2001 epub ahead of print.
- Voon P, Callon C, Nguyen P, Dobrer S, Montaner J, Wood E, Kerr T. Self-management of pain among people who inject drugs in Vancouver. *Pain Manag*. 2014; 4:27–35. [PubMed: 24641341]
- Voon P, Callon C, Nguyen P, Dobrer S, Montaner J, Wood E, Kerr T. Denial of prescription analgesia among people who inject drugs in a Canadian setting. *Drug Alcohol Rev*. 2015; 34:221–228. [PubMed: 25521168]
- Werb D, Kerr T, Buxton J, Shoveller J, Richardson C, Montaner J, Wood E. Crystal methamphetamine and initiation of injection drug use among street-involved youth in a Canadian setting. *CMAJ*. 2013; 185:1569–1575. [PubMed: 24130244]
- Wood E, Stoltz J, Montaner J, Kerr T. Evaluating methamphetamine use and risks of injection initiation among street youth: the ARYS study. *Harm Reduct J*. 2006; 3:1–6. [PubMed: 16403229]
- Young AM, Havens JR. Transition from first illicit drug use to first injection drug use among rural Appalachian drug users: a cross-sectional comparison and retrospective survival analysis. *Addiction*. 2012; 107:587–596. [PubMed: 21883604]

Table 1

Baseline characteristics of study sample, stratified by any PO injection over the study period.

Characteristic	Total n = 1580 (%)	PO injection		p-value
		Yes n = 247 (15.6%)	No n = 1333 (84.4%)	
Gender				
Female	521 (33.0)	89 (36.0)	432 (32.4)	0.266
Male	1059 (67.0)	158 (64.0)	901 (67.6)	
Age				
Median (IQR [*])	32.2 (22.4–44.6)	37.0 (24.4 – 44.1)	29.4 (22.1 – 44.7)	0.003 [†]
Ethnicity				
Caucasian	886 (56.1)	157 (63.6)	729 (54.7)	0.010
Other	694 (43.9)	90 (36.4)	604 (45.3)	
Education				
Secondary	675 (42.7)	127 (51.4)	548 (41.1)	0.004
<Secondary	874 (55.3)	118 (47.8)	756 (56.7)	
Downtown Eastside [‡]				
Yes	777 (49.2)	153 (61.9)	624 (46.8)	<0.001
No	803 (50.8)	94 (38.1)	709 (53.2)	
Incarcerated [‡]				
Yes	222 (14.1)	39 (15.8)	183 (13.7)	0.396
No	1337 (84.6)	305 (83.0)	1132 (84.9)	
Homeless [‡]				
Yes	722 (45.7)	98 (39.7)	624 (46.8)	0.034
No	853 (54.0)	149 (60.3)	704 (52.8)	
Addiction treatment [‡]				
No treatment	960 (60.8)	109 (44.1)	851 (63.8)	<0.001
Non-methadone	245 (15.5)	32 (13.0)	213 (16.0)	
Methadone	35 (2.2)	8 (3.2)	27 (2.0)	
Methadone and non-methadone	316 (20.0)	92 (37.3)	224 (16.8)	
Drug dealing [‡]				
Yes	547 (34.6)	107 (43.3)	440 (33.0)	0.002
No	1033 (65.4)	140 (56.7)	893 (67.0)	
Sex work [‡]				
Yes	174 (11.0)	25 (10.1)	149 (11.2)	0.680
No	1394 (88.2)	217 (87.9)	1177 (88.3)	
Heavy alcohol use [‡]				
Yes	427 (27.0)	41 (16.6)	386 (29.0)	<0.001
No	1153 (73.0)	206 (83.4)	947 (71.0)	
Heroin injection [‡]				
Yes	395 (25.0)	134 (54.3)	261 (19.6)	<0.001

Characteristic	Total n = 1580 (%)	PO injection		p-value
		Yes n = 247 (15.6%)	No n = 1333 (84.4%)	
No	1185 (75.0)	113 (45.7)	1072 (80.4)	
Heroin non-injection [‡]				
Yes	221 (14.0)	42 (17.0)	179 (13.4)	0.151
No	1348 (85.4)	205 (83.0)	1143 (85.7)	
Cocaine injection [‡]				
Yes	375 (23.7)	95 (38.5)	280 (21.0)	<0.001
No	1205 (76.3)	152 (61.5)	1053 (79.0)	
Crack/cocaine non-injection [‡]				
Yes	1188 (75.2)	200 (81.0)	988 (74.1)	0.029
No	386 (24.4)	47 (19.0)	339 (25.4)	
Methamphetamine injection [‡]				
Yes	154 (9.7)	38 (15.4)	116 (8.7)	0.001
No	1426 (90.3)	209 (84.6)	1217 (91.3)	
Methamphetamine non-injection [‡]				
Yes	355 (22.5)	49 (19.8)	306 (23.0)	0.256
No	1215 (76.9)	198 (80.2)	1017 (76.3)	
PO non-injection [‡]				
Yes	90 (5.7)	12 (4.9)	78 (5.9)	0.508
No	1473 (93.2)	235 (95.1)	1238 (92.9)	
Marijuana use [‡]				
Yes	1064 (67.3)	153 (61.9)	911 (68.3)	0.040
No	511 (32.3)	94 (38.1)	417 (31.3)	
Sexual abuse [‡]				
Yes	361 (22.8)	64 (25.9)	297 (22.3)	0.246
No	1153 (73.0)	175 (70.9)	978 (73.4)	
Suicide attempt [‡]				
Yes	76 (4.8)	12 (4.9)	64 (4.8)	0.965
No	1487 (94.1)	232 (93.9)	1255 (94.1)	
Cohort				
ACCESS	409 (25.9)	64 (25.9)	345 (25.9)	<0.001
ARYS	643 (40.7)	60 (24.3)	583 (43.7)	
VIDUS	528 (33.4)	123 (49.8)	405 (30.4)	

* IQR = Interquartile Range.

[‡] Wilcoxon rank-sum test was used to obtain estimate.

[‡] Refers to behaviours/exposures in the previous six months.

Table 2

Unadjusted and adjusted hazard ratios for factors related to initiation of prescription opioid injection among people who use drugs in Vancouver (n= 1580).

Variable	Hazard Ratio (95% CI)*			
	Unadjusted	p-value	Adjusted	p-value
Sex (Female vs. Male)	1.11 (0.86–1.44)	0.421		
Age (Per year older)	1.00 (0.99–1.01)	0.654		
Ethnicity (Caucasian vs. Non-Caucasian)	1.51 (1.16–1.96)	0.002	1.37 (1.04–1.79)	0.024
Education (Sec. vs. < Sec.)	1.38 (1.07–1.77)	0.012	1.44 (1.12–1.87)	0.005
Follow-up Period (per 6-month interview interval)	0.95 (0.91–0.99)	0.008	0.97 (0.93–1.00)	0.063
Cohort				
ACCESS (vs. ARYS)	1.26 (0.88–1.79)	0.207		
VIDUS (vs. ARYS)	1.73 (1.25–2.40)	<0.001		
Downtown Eastside Residency**	1.85 (1.42–2.40)	<0.001	1.31 (1.00–1.71)	0.047
Homelessness**	1.19 (0.91–1.56)	0.213		
Incarcerated**	1.29 (0.91–1.84)	0.158		
Addiction Treatment Enrolment**				
Non-methadone treatment (vs. none)	1.20 (0.80–1.81)	0.383	1.16 (0.76–1.75)	0.498
Methadone treatment (vs. none)	4.46 (2.03–9.80)	<0.001	2.96 (1.34–6.51)	0.007
Methadone and non-methadone (vs. none)	2.45 (1.85–3.24)	<0.001	1.37 (1.03–1.82)	0.031
Drug Dealing**	1.76 (1.34–2.31)	<0.001	1.32 (1.00–1.76)	0.050
Sex work**	1.05 (0.68–1.64)	0.824		
Heavy Alcohol Use**	0.78 (0.57–1.07)	0.121		
Heroin Injection**	6.30 (4.83–8.20)	<0.001	4.39 (3.24–5.95)	<0.001
Heroin Non-injection**	1.54 (1.06–2.23)	0.023		
Cocaine Injection**	2.23 (1.71–2.89)	<0.001	1.40 (1.06–1.84)	0.018
Crack/coc. Non-injection**	1.69 (1.25–2.28)	<0.001		
Methamphetamine Injection**	2.16 (1.56–3.00)	<0.001	1.71 (1.22–2.39)	0.002
Methamphetamine Non-injection**	0.91 (0.64–1.30)	0.619		
Prescription Opioid Non-injection**	1.94 (1.22–3.09)	0.005	1.99 (1.25–3.17)	0.004
Marijuana Use**	1.04 (0.80–1.35)	0.773		
Sexual Abuse**	1.12 (0.84–1.49)	0.441		
Suicide Attempt**	1.56 (0.85–2.87)	0.150		

* 95% Confidence Interval.

** In the previous six months (yes vs. no), lagged to the previous follow-up to prescription opioid injection initiation assessment.

Table 3

Top: Patterns of heroin use before and after initiating prescription opioid injection among initiators (n = 218) and a group of controls matched on initiation period (n = 872); *Bottom:* Results of four linear growth curve analyses comparing initiators with controls for each heroin use pattern.

Heroin use [*]	PO Initiation Period		<i>p</i> value
	Before n (%)	After n (%)	
Daily injection			
PO initiators	62 (28.4)	77 (35.3)	0.075
Controls	53 (6.1)	48 (5.5)	0.466
Any injection			
PO initiators	135 (61.9)	149 (68.4)	0.090
Controls	148 (17.0)	133 (15.3)	0.147
Daily non-injection			
PO initiators	5 (2.3)	4 (1.8)	0.706
Controls	12 (1.4)	8 (0.9)	0.248
Any non-injection			
PO initiators	27 (12.4)	29 (13.3)	0.758
Controls	73 (8.4)	47 (5.4)	0.002

Heroin use [*]	Slope (95% CI ^{**})	<i>p</i> value ^{***}
Daily injection		
PO initiators	0.592 (0.046–1.138)	0.049
Controls	−0.157 (−0.660–0.346)	
Any injection		
PO initiators	0.639 (0.072–1.205)	0.011
Controls	−0.239 (−0.605–0.127)	
Daily non-injection		
PO initiators	−0.369 (−2.051–1.312)	0.901
Controls	−0.498 (−1.640–0.644)	
Any non-injection		
PO initiators	0.068 (−0.651–0.787)	0.065
Controls	−0.751 (−1.240 to−0.262)	

* In the previous 6 months.

** 95% Confidence Interval.

*** Estimates have been adjusted for age, gender, ethnicity, and baseline education, Downtown Eastside residency, addiction treatment, drug dealing, heavy alcohol use, cocaine injection, crack/cocaine non-injection, methamphetamine injection, and cohort membership.