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Initiation into heroin use among street-involved youth in a Canadian setting: A longitudinal cohort study

Julia Goldman-Hasbun[a], Thomas Kerr[a,b], Ekaterina Nosova[a], Hennady Shulha[a], Evan Wood[a,b], Kora DeBeck[a,c,*]

[a] B.C. Centre on Substance Use, 400 - 1045 Howe Street, Vancouver, BC V6Z 2A9, Canada
[b] Department of Medicine, University of British Columbia, St. Paul's Hospital, 608-1081 Burrard Street, Vancouver, BC V6Z 1Y6, Canada
[c] School of Public Policy, Simon Fraser University, 515 West Hastings Street, Vancouver, BC V6B 5K3, Canada

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ABSTRACT

Background: Emerging evidence suggests that non-medical prescription opioid (NMPO) use may be a risk factor for initiating heroin use; however, pathways from PO to heroin use among youth remain underexplored. We sought to examine the association between NMPO use and heroin initiation.
Methods: Between September 2005 and June 2017 data were derived from an open prospective cohort of street-involved youth aged 14–28 who use illegal drugs in Vancouver, Canada. The study included 526 youth who had never used non-injection heroin, and 652 youth who had never used injection heroin at baseline. We used Cox proportional hazards regressions to examine the association between NMPO use – in addition to other substance use patterns – and subsequent initiation into non-injection and injection heroin use.
Results: Among those who had never used non-injection heroin at baseline, 133 (25.3%) initiated non-injection heroin use during the study period. Among those who had never injected heroin at baseline, 137 (21.0%) initiated heroin injection during the study period. In multivariable analyses, NMPO use, crack use, and crystal methamphetamine use predicted non-injection heroin initiation (all $p < 0.05$). In separate multivariable analyses, non-injection heroin and crystal methamphetamine predicted heroin injection initiation (all $p < 0.05$).
Conclusions: Among street-involved youth in this setting, NMPO use predicted initiation into non-injection heroin use but not initiation into heroin injection. Interestingly, crack cocaine and crystal methamphetamine use were stronger predictors of heroin initiation than NMPO use was, suggesting that stimulant use may carry greater risks for heroin initiation than NMPO use.

1. Introduction

Prescription opioid-related morbidity and mortality has increased dramatically throughout North America in recent years. Among Canadian youth, rates of non-medical prescription opioid (NMPO) use are nearly six times higher than among adults (Health Canada, 2012). Within North American settings, several policies and programs have aimed to reduce inappropriate opioid prescribing, (e.g., prescription-drug monitoring programs) and there is some evidence of their success in reducing rates of deaths from overdose (Compton et al., 2016). However, somewhat in parallel to the increase in NMPO use and associated harms, rates of heroin use and heroin-related mortality in North American settings have also been increasing (Compton et al., 2016).

There is evidence indicating that NMPO use may prompt transitions to heroin use among young populations (Cerdá et al., 2015; Lankenau et al., 2012a; Palamar et al., 2016; Peavy et al., 2012; Pollini et al., 2011), and that transitions from NMPO use to heroin use elevate the risk of exposure to a range of harms (Daniulaityte et al., 2009; Grau et al., 2007; Lankenau et al., 2012a, 2012b; Peavy et al., 2012). Some studies have suggested that most people who transition from NMPO use to heroin use begin by using oral POs, and that pathways into injection heroin use may be driven by higher developed opioid tolerance, increased availability, and lower cost of heroin relative to POs, as well as exposure to riskier drug environments (Cicero et al., 2014; Compton et al., 2016; Inciardi et al., 2009; Lankenau et al., 2012b; Mars et al., 2014; Mateu-Gelabert et al., 2015; Pollini et al., 2011). This transition may occur among both those who use medical POs and non-medical POs, although only a small number of PO users transition to heroin use (Kolodny et al., 2015), with NMPO acting as either a pathway between

* Corresponding author at: B.C. Centre on Substance Use, 400 - 1045 Howe Street, Vancouver, BC V6Z 2A9, Canada.
E-mail address: kdebeck@sfu.ca (K. DeBeck).

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medical POs and heroin or as a first point of initiation into opioid use through diverted POs. While a positive correlation between NMPO use and heroin use among youth has been established, pathways between NMPO use and heroin use remain poorly characterized. Understanding these complex drug use trajectories may inform prevention efforts and policy addressing opioid use among young people.

The current study aimed to examine whether non-injection NMPO use predicts initiation into either injection or non-injection heroin use among a population of street-involved adolescents and young adults (referred to as youth) who use illegal drugs in Vancouver, Canada. Recent studies within the same setting have found past-six-month use of opioids to be approximately 70% for injection heroin (Hadland et al., 2017), 35% for non-injection heroin (Hadland et al., 2017), and 10% for NMPOs (Lake et al., 2018a). Unfortunately, barriers to addiction treatment among this population have also been well-described (Phillips et al., 2015).

2. Material and methods

2.1. Design

The At-Risk Youth Study (ARYS) is an open prospective cohort study of street-involved youth who use illegal drugs based in Vancouver, Canada. Youth aged 14–28 who have used any drug (other than or in addition to cannabis) in the preceding 30 days are eligible for study enrollment. Recruited youth are street-involved at baseline, defined as being without stable housing or having accessed street-based services in the preceding six months (Boivin et al., 2005; DeMatteo et al., 1999; Kerr et al., 2009a). The study period was between September 2005 and June 2017.

Street-based outreach is used to enhance recruitment both during daytime and nighttime hours in various neighborhoods where street youth congregate. Snowball sampling is also used to maximize enrollment. After providing informed consent, participants complete an interviewer-administered questionnaire regarding sociodemographic details, engagement with health and social services, substance use, and other behaviors. Participants are provided with compensation for their time ($30 CAN). Individuals are then requested to return to the study site every six months throughout the study. At each follow-up, a follow-up questionnaire is administered. ARYS is approved by the University of British Columbia and Providence Health Care Research Ethics Board. The study has been described in more detail previously (Wood et al., 2006).

Two primary separate analyses were conducted. The first primary analysis (referred to as analysis one) assessed initiation into non-injection heroin use. The second primary analysis (referred to as analysis two) assessed initiation into injection heroin use. To examine the relationship between NMPO use and initiation into non-injection heroin use, participants who reported never having used non-injection heroin at baseline (i.e., those who responded “no” to the question: “have you ever used non-injection heroin [sniffed or snorted]?”), and later completed at least one follow-up visit during the study, were included in analysis one. To examine the potential relationship between NMPO use and initiation into injection heroin, participants who reported having never injected heroin at baseline (i.e., those who responded “no” to the question: “have you ever injected heroin?”), and later completed at least one follow-up visit during the study, were included in analysis two. It should be noted that when POs are not directly obtained from a pharmacy or hospital, it may be challenging to distinguish between legally and illegally–manufactured opioids. There is a growing market of illegally-manufactured synthetic opioids, which are sometimes marketed and sold as pharmaceutical-grade legally-manufactured POs. Moreover, there has been a sharp increase in the presence of Fentanyl in street drugs, such as heroin, which spiked in BC around 2016 (BC Coroners Service, 2019). Therefore, there is potential for misclassification for both heroin and NMPOs.

The primary outcome of interest for analysis one was initiation into non-injection (e.g., snorting, inhaling, oral intake, smoking) heroin, and the primary outcome of interest for analysis two was initiation into injection heroin (note that non-injection and injection heroin may be identical in substance, the distinction refers solely to the route of administration). In both analyses, participants may or may not have used NMPOs over the course of the study. To assess the outcomes of interest, we asked participants at each follow-up to indicate if they had used non-injection or injection heroin [yes vs. no] in the previous six months. Initiation into heroin use was determined from the follow-up period corresponding with the first report of heroin use (non-injection or injection respectively).

2.2. Measures

The primary explanatory variable of interest for both analyses was time-updated and defined as non-injection NMPO use in the last six months [yes vs. no]. The list of POs provided underwent periodic modifications to reflect current trends in PO availability. The most recent questionnaire included options for OxyNeo, OxyContin, and Percocet (i.e. oxycodone); Tylenol 3 (i.e., codeine); morphine, Dilaudid (i.e., hydromorphone); Demerol (i.e., meperidine); methadone, fentanyl; Vicodin (i.e., hydrocodone); Talwin (i.e., pentazocine); and Tramadol. Participants could also specify any POs they used that were not included on the list. The survey specified that these POs were used without a medical prescription or only for the feeling they caused.

To determine whether there was a significant relationship between our main explanatory variable (NMPO use) and outcomes of interest (non-injection and injection heroin initiation respectively), we a priori selected various potential confounding variables, which we hypothesized might be associated with both NMPO use and heroin initiation. Potential confounders included demographic variables and drug use patterns which, based on the literature, are known to be associated with drug use trajectories (Baldwin et al., 2013; Lankenau et al., 2012b; Mars et al., 2014). These were: current age [per year older]; male gender (self-identified at baseline) [yes vs. no]; white ethnicity/race (self-identified at baseline) [yes vs. no], high school completion (or currently enrolled) [yes vs. no], living in Downtown Eastside neighborhood (a low-income area in Vancouver with an open drug market, high levels of substance use and homelessness, communicable disease, and crime (Linden et al., 2013)) [yes vs. no] (note that participants living in the Downtown Eastside may been homeless, unstably housed, or permanently housed); homelessness [yes vs. no]; incarceration (defined as being in detention, prison, or jail overnight or longer) [yes vs. no]; sex work (ever received money, gifts, food, shelter, clothes, or drugs in exchange for sex) [yes vs. no]; crystal methamphetamine use (yes vs. no); crack or cocaine use (yes vs. no); daily cannabis use (yes vs. no); heavy alcohol use (defined as: > 14 drinks/week or > 4 drinks on 1 occasion for men, and > 7 drinks/week or > 3 drinks on 1 occasion for women (Willenbring et al., 2009)) [yes vs. no]; engagement with drug or alcohol treatment (any of: detox, daytox, recovery house, treatment center, counsellor, NA/CA/AA/SMART, methadone/methadose program, suboxone treatment, onsite treatment, residential community, out-patient treatment, drug treatment court, or other) [yes vs. no]; and drug dealing in the last six months (defined as selling drugs as a source of income) [yes vs. no]. Unless otherwise specified, all variables refer to the last six months.

Some participants in analysis one (who were non-injection heroin-naïve at baseline) had used heroin via injection, and so we adjusted for injection heroin use [yes vs. no] in this analysis. Similarly, some participants in analysis two (who were injection heroin-naïve at baseline) had used non-injection heroin, and so we adjusted for non-injection heroin use [yes vs. no] in this analysis.

We also controlled for childhood maltreatment, derived from the Childhood Trauma Questionnaire (CTQ), which has been shown to be valid and reliable among substance-using youth (Bernstein et al., 2003;

Fink et al., 1995). The CTQ is a 28-item survey that measures the following five forms of maltreatment: physical abuse, sexual abuse, emotional abuse, physical neglect, and emotional neglect. Subscales on the CTQ survey with predetermined cut-off scores were used to define trauma levels for each form of maltreatment. The four levels of trauma are: none, low, moderate, and severe. As in previous work, we have collapsed the trauma levels into two categories 'none/low' and 'moderate/severe' (DeBeck et al., 2013; Kerr et al., 2009b; Stoltz et al., 2007).

2.3. Analyses

For analyses one and two, we initially examined baseline characteristics of participants stratified by the outcome of interest (initiation into non-injection heroin use for analysis one and initiation into heroin injection for analysis two) using Pearson's chi-square test for dichotomous variables, Wilcoxon rank sum test for continuous variables, and Fisher's test in cases when counts were < 5. We calculated the incidence density of initiation into non-injection and injection heroin use using person-time methods and the Poisson distribution to estimate 95% confidence intervals. The cumulative incidence of initiation into non-injection (analysis one) and injection heroin use (analysis two) from the time of study enrolment stratified by NMPO use was calculated using Kaplan-Meier estimates. Subsequently, we used Cox models to estimate the unadjusted hazard ratios and 95% confidence intervals for factors associated with each of our outcomes of interest (Kleinbaum and Klein, 2010). All sociodemographic variables – including Downtown Eastside residence and homelessness – and substance use-related covariates were time-updated in order to account for changes over time. In addition, our substance use variables were lagged to the prior study visit to protect against reverse causation. Both the first event and recurrent events of heroin initiation were considered in these analyses.

To fit our multivariable Cox models, we used a previously described backwards selection process (Maldonado and Greenland, 1993; Rothman et al., 2008). We began with all variables in a full model, then generated a series of reduced models by removing each secondary explanatory variable one at a time. For each of these models, we assessed the relative change in the coefficient for our primary explanatory variables. The secondary explanatory variable of interest that resulted in the smallest absolute relative change in the coefficient for NMPO use was then removed. Secondary variables continued to be removed through this process until the smallest relative change exceeded 5%. Remaining variables were considered confounders and were included in the final multivariable model. All statistical analyses were performed using R, version 3.5.0 (R Foundation for Statistical Computing, Vienna, Austria). All p-values were two-sided and tests were considered significant at $p < 0.05$ level.

To estimate the reduction in non-injection heroin and injection heroin initiation events that could occur among street-involved youth if risk factors found to be associated with heroin initiation were eliminated, attributable risk percentage (AR%) and population attributable risk percentage (PAR%) measures were also calculated (Cole and MacMahon, 1971, pp. 242–244). The relevance of attributable risk measures in prevention planning has been previously described (Hagan, 2003; Northridge, 1995). The AR% refers to the estimated percentage of heroin initiation events attributable to the exposure of interest among those exposed to the risk factor, while the PAR% refers to the estimated percentage of heroin initiation events attributable to the exposure of interest within the underlying population of street-involved youth.

We also ran four separate Cox regression sub-analyses that looked at injection NMPO use and 'any' NMPO use (non-injection and injection combined): 1) injection NMPO use as a predictor of non-injection heroin initiation; 2) injection NMPO use as a predictor of injection heroin initiation; 3) 'any' NMPO use as a predictor of non-injection heroin initiation; and 4) 'any' NMPO use as a predictor of injection heroin initiation. Additionally, we ran two Cox regression sub-analyses identical to our two primary analyses (described above), adding the variables 'daily' crystal methamphetamine use and 'daily' polydrug use in order to examine whether high frequency of crystal methamphetamine use and polysubstance use would be significantly associated with our outcomes of interest. Further, we ran two sensitivity analyses identical to our primary analyses, which excluded participants who only had two follow-up visits and excluded events where the median time from last study visit to report if initiation was over 12 months. Moreover, we tested the two models for period effects by including a variable accounting for year of transition into heroin use.

3. Results

3.1. Participants

Between December 2005 and June 2017, of 1399 ARYS participants, 526 (37.6%) reported never having used non-injection heroin at baseline and returned for at least one study follow-up to assess for initiation (analysis one), and 652 (46.6%) participants reported never having injected heroin at baseline and returned for at least one study follow-up to assess for initiation (analysis two).

Among the youth in the sample used in analysis one ($n = 526$), 353 (67.1%) identified as male and the median age was 21.6 (interquartile range [IQR]: 19.8–23.3). This sample contributed 2790 observations to the analysis. The median number of study visits for this sample was 4 (IQR: 3–6), and the median time between visits was 5.95 (5.0–7.1) months. The average yearly loss to follow up rate during the study period among the participants in first sample was 7.8%.

Among the youth in the sample used in analysis two ($n = 652$), 454 (69.6%) identified as male, the median age was 21.7 (IQR: 19.8–23.5), and this sample contributed 3552 observations. The median number of study visits for this sample was 4 (IQR: 3–7), and the median time between visits was 5.95 (5.2–7.2) months. The average yearly loss to follow up rate during the study period among the participants in the second sample was 8.0%.

Compared to the analytic samples, participants who met the same eligibility criteria but were excluded from the analyses due to insufficient follow-up were less likely to use crack cocaine. This was true for both the sample in analysis one (60.9% vs. 70.9%, $p = 0.009$) and the sample in analysis two (65.9% vs. 73.8%, $p = 0.015$). However, excluded participants did not differ significantly from the analytic samples in terms of sociodemographic characteristics or other measures of substance use.

3.2. Rates of heroin initiation

Over study follow-up, among 526 participants who had never used non-injection heroin at baseline, 133 (25%) subsequently reported initiation into non-injection heroin use. The median time to non-injected heroin initiation was 17.47 months (IQR: 3.60–39.58) and the observed incidence density was 9.02 cases per 100 person years [95% Confidence Interval (CI): 4.34–16.25]. Among the 625 participants who had never injected heroin at baseline, 137 (22%) subsequently reported initiation into injection heroin. The median time to injection heroin initiation was 15.2 months (IQR: 4.90–40.60) and the observed incidence density was 7.24 cases per 100 person years [95% Confidence Interval (CI): 3.16–13.86].

The rates of non-injection heroin initiation events among the sample in analysis one (non-injection heroin-naïve at baseline) increased from an average of 6% per year between 2006–2011 to 15% per year between 2012–2017. There was also an increase in the rates of injection heroin initiation events: heroin injection initiation events among the sample in analysis two (injection heroin naïve at baseline) increased from an average of 6% per year between 2006–2011 to 11% per year between 2012–2017. In analysis one, we also observed an increased in

Table 1
Baseline characteristics of 526 street-involved youth who were non-injection heroin-naïve at baseline, stratified by initiation into non-injection heroin over study follow-up.

Characteristic[a]	Total (%) (n = 526)	Initiated into non-injection heroin during follow-up		Odds Ratio[b] (95% CI)
		Yes (%) (n = 133)	No (%) (n = 393)	
Sociodemographic factors				
Age, per year older (median, IQR)	21.6 (19.8–23.3)	21.5 (19.7–22.8)	21.6 (19.8–23.5)	0.84 (0.56–1.24)
Gender (male vs. female)[c]	353 (67.1)	86 (64.7)	267 (67.9)	0.82 (0.54–1.24)
White ethnicity/race (yes vs. no)[c]	352 (66.9)	84 (63.2)	268 (68.2)	0.80 (0.53–1.21)
High school completion (yes vs. no)	246 (46.8)	50 (37.6)	196 (49.9)	0.62 (0.41–0.92)
DTES residence (yes vs. no)[d]	126 (24.0)	38 (28.6)	88 (22.4)	1.39 (0.89–2.16)
Homelessness (yes vs. no)[d]	375 (71.3)	98 (73.7)	277 (70.5)	1.19 (0.76–1.85)
Incarceration (yes vs. no)[d]	83 (15.8)	26 (19.5)	57 (14.5)	1.45 (0.87–2.42)
Sex work (yes vs. no)[d]	31 (5.9)	11 (8.3)	20 (5.1)	1.68 (0.78–3.61)
Substance use–related behaviors[d] (yes vs. no)				
Any NMPO use	75 (14.3)	18 (13.5)	57 (14.5)	0.95 (0.53–1.68)
Non-injection NMPO use	48 (9.1)	8 (6.0)	40 (10.2)	0.58 (0.26–1.27)
Injection NMPO use	31 (5.9)	10 (7.5)	21 (5.3)	1.44 (0.66–3.13)
Injection heroin use	74 (14.1)	22 (16.5)	52 (13.2)	1.30 (0.76–2.24)
Crystal methamphetamine use	221 (42.0)	72 (54.1)	149 (37.9)	2.08 (1.39–3.12)
Crack cocaine use	373 (70.9)	104 (78.2)	269 (68.4)	1.81 (1.12–2.93)
Daily cannabis use	235 (44.7)	57 (42.9)	178 (45.3)	0.94 (0.63–1.41)
Heavy alcohol use	212 (40.3)	56 (42.1)	156 (39.7)	1.13 (0.76–1.70)
Drug or alcohol treatment	131 (24.9)	46 (34.6)	85 (21.6)	1.96 (1.27–3.03)
Drug dealing	225 (42.8)	60 (45.1)	165 (42.0)	1.14 (0.76–1.69)
Childhood trauma (Moderate/severe vs. none/low)				
Sexual abuse	95 (18.1)	27 (20.3)	68 (17.3)	1.23 (0.74–2.03)
Physical abuse	149 (28.3)	45 (33.8)	104 (26.5)	1.43 (0.93–2.20)
Emotional abuse	231 (43.9)	65 (48.9)	166 (42.2)	1.33 (0.88–2.00)
Physical neglect	149 (28.3)	50 (37.6)	99 (25.2)	1.82 (1.18–2.78)
Emotional neglect	229 (43.5)	66 (49.6)	163 (41.5)	1.47 (0.97–2.22)

CI: Confidence Interval; IQR: Interquartile range; DTES: Downtown Eastside; NMPO: Non-medical prescription opioids.
[a] Yes vs. no, except for age and childhood trauma-related variables.
[b] Unadjusted.
[c] Self-identified.
[d] During the six months preceding study enrollment.

crystal methamphetamine initiation, from 31% per year between 2006–2011 to 51% per year between 2012–2017.

3.3. Predictors of heroin initiation

Baseline characteristics of the non-injection heroin-naïve sample (analysis one) stratified by subsequent initiation into non-injection heroin are presented in Table 1. Baseline characteristics of the injection heroin-naïve sample (analysis two) stratified by initiation into injection heroin are presented in Table 2.

Table 3 shows the unadjusted and adjusted hazard ratios of initiation into non-injection heroin (analysis one). NMPO use was significantly associated with non-injection heroin initiation in both bivariable [hazard ratio (HR): 2.16, 95% CI: 1.28–3.66] and multivariable Cox regressions [adjusted hazard ratio (AHR): 1.86, 95% CI: 1.09–3.19] after adjustment for potential confounders. Crystal methamphetamine [AHR: 2.70, 95% CI: 1.88–3.88] and crack cocaine [AHR: 2.30, 95% CI: 1.52–3.49] were also associated with initiation into non-injection heroin.

Table 4 shows the unadjusted and adjusted hazard ratios of initiation into injection heroin (analysis two). NMPO use was significantly associated with initiation into heroin injection in the bivariable Cox regression [HR: 1.68, CI: 1.03–2.74], but was no longer associated with heroin injection initiation after adjustment for confounders. In the multivariable Cox regression model, crystal methamphetamine [AHR: 1.99, CI: 1.38–2.88] and non-injection heroin [AHR: 1.93, CI: 1.25–2.97] were associated with initiation into heroin injection.

In sub-analyses (not shown) examining injection NMPO use and 'any' NMPO use (injection and non-injection combined), we did not find any significant associations between the exposures and outcomes of interest (all $p > 0.05$). Additionally, in other sub-analyses using samples from analyses one and two that included a 'daily' methamphetamine use and a polydrug use variable, we did not find any significant associations between daily methamphetamine use or polydrug use and our outcomes of interest (non-injection heroin initiation and injection heroin initiation) (all $p > 0.05$). Further, in our sensitivity analyses that excluded participants who had only two follow-up visits and excluded events where the median time from last study visit to report of initiation was over 12 months (not shown), no meaningful changes between our exposures and outcomes of interest were observed. In our models that tested for period effects (not shown), we found that year of transition was not significantly associated with heroin initiation ($p > 0.05$ for both models) and did not impact the key findings of the study.

3.4. Attributable risk calculations

The results of the attributable risk calculations are presented in Table 5. Among the underlying population of street-involved youth, 4% of non-injection heroin initiation events may be attributable to NMPO use, 26% of non-injection heroin initiation events may be attributable to crystal methamphetamine use, and 40% of non-injection heroin initiation events may be attributable to crack cocaine use. Further, 23% of injection heroin initiation events may be attributable to crystal methamphetamine use, and 10% of heroin injection initiation events may be attributable to non-injection heroin use in the underlying population of street-involved youth. Because the assumption of a causal relationship between the risk factor and the outcome is needed to calculate a valid population attributable risk percentage (Rockhill et al., 1998), variables that were not lagged (e.g., homelessness, DTES residence) or not significantly associated with heroin initiation in the Cox regression models were not included in Table 5.

Table 2
Baseline characteristics of 652 street-involved youth who were injection heroin-naïve at baseline, stratified by initiation into injection heroin over study follow-up.

		Initiated into injection heroin during follow-up		
Characteristic[a]	Total (%) (n = 652)	Yes (%) (n = 137)	No (%) (n = 515)	Odds Ratio[b] (95% CI)
Sociodemographic factors				
Age, per year older (median, IQR)	21.7 (19.8–23.5)	21.4 (19.4–22.7)	21.8 (19.9–23.6)	0.94 (0.88–1.01)
Male gender (yes vs. no)[c]	454 (69.6)	98 (71.5)	356 (69.1)	1.08 (0.71–1.64)
White ethnicity/race (yes vs. no)[c]	429 (65.8)	90 (65.7)	339 (65.8)	0.97 (0.65–1.44)
High school completion (yes vs. no)	303 (46.5)	50 (36.5)	253 (49.1)	0.60 (0.40–0.88)
DTES residence (yes vs. no)[d]	162 (24.8)	35 (25.5)	127 (24.7)	1.05 (0.68–1.62)
Homelessness (yes vs. no)[d]	469 (71.9)	99 (72.3)	370 (71.8)	1.08 (0.70–1.65)
Incarceration (yes vs. no)[d]	106 (16.3)	29 (21.2)	77 (15.0)	1.52 (0.94–2.45)
Sex work (yes vs. no)[d]	44 (6.7)	12 (8.8)	32 (6.2)	1.45 (0.73–2.89)
Substance use-related behaviors[d] (yes vs. no)				
Any NMPO use	92 (14.1)	24 (17.5)	68 (13.2)	1.39 (0.84–2.32)
Non-injection NMPO use	88 (13.5)	22 (16.1)	66 (12.8)	1.30 (0.77–2.20)
Injection NMPO use	8 (1.2)	3 (2.2)	5 (1.0)	2.28 (0.35–11.87)
Non-injection heroin use	133 (20.4)	43 (31.4)	90 (17.5)	2.20 (1.43–3.38)
Crystal methamphetamine use	299 (45.9)	84 (61.3)	215 (41.7)	2.31 (1.56–3.41)
Crack cocaine use	481 (73.8)	106 (77.4)	375 (72.8)	1.34 (0.85–2.10)
Daily cannabis use	311 (47.7)	75 (54.7)	236 (45.8)	1.47 (1.01–2.16)
Heavy alcohol use	254 (39)	49 (35.8)	205 (39.8)	0.84 (0.56–1.24)
Drug or alcohol treatment	175 (26.8)	43 (31.4)	132 (25.6)	1.32 (0.87–2.00)
Drug dealing	303 (46.5)	70 (51.1)	233 (45.2)	1.26 (0.87–1.84)
Childhood trauma (Moderate/severe vs. none/low)				
Sexual abuse	112 (17.2)	29 (21.2)	83 (16.1)	1.39 (0.86–2.25)
Physical abuse	184 (28.2)	47 (34.3)	137 (26.6)	1.45 (0.96–2.18)
Emotional abuse	275 (42.2)	59 (43.1)	216 (41.9)	1.02 (0.68–1.51)
Physical neglect	191 (29.3)	45 (32.8)	146 (28.3)	1.25 (0.82–1.89)
Emotional neglect	281 (43.1)	70 (51.1)	211 (41.0)	1.57 (1.05–2.34)

CI: Confidence Interval; IQR: Interquartile range; DTES: Downtown Eastside; NMPO: Non-medical prescription opioids.
[a] Yes vs. no, except for age and childhood trauma-related variables.
[b] Unadjusted.
[c] Self-identified.
[d] During the six months preceding study enrollment.

Table 3
Unadjusted and adjusted hazard ratios (HRs) for factors associated with non-injection heroin initiation, when NMPO use includes non-injection NMPO use only, among street-involved youth (n = 526).

		Hazard Ratios (HR)		
Characteristic[a]	Unadjusted HR (95% CI)	p-value	Adjusted HR[b] (95% CI)	p-value
Sociodemographic factors				
Age (per year older)	0.97 (0.91–1.04)	0.375		
Gender (male vs. female)[c]	0.80 (0.56–1.15)	0.221		
White ethnicity/race (yes vs. no)[c]	0.94 (0.66–1.33)	0.709		
High school completion (yes vs. no)	0.72 (0.51–1.02)	0.063		
DTES residence (yes vs. no)[d]	2.23 (1.59–3.14)	< 0.001	1.94 (1.35–2.79)	< 0.001
Homelessness (yes vs. no)[d]	2.61 (1.82–3.74)	< 0.001		
Incarceration (yes vs. no)[d]	1.79 (1.21–2.64)	0.003		
Sex work (yes vs. no)[d]	3.87 (2.13–7.03)	< 0.001		
Substance-use related behaviors[d,e] (yes vs. no)				
Non-injection NMPO use	2.16 (1.28–3.66)	0.004	1.86 (1.09–3.19)	0.024
Injection heroin use	2.10 (1.34–3.29)	0.001		
Crack cocaine use	2.29 (1.55–3.40)	< 0.001	2.30 (1.52–3.49)	< 0.001
Crystal methamphetamine use	2.19 (1.42–3.37)	< 0.001	2.70 (1.88–3.88)	< 0.001
Daily cannabis use	0.99 (0.69–1.41)	0.946		
Heavy alcohol use	0.93 (0.65–1.34)	0.721		
Drug or alcohol treatment	1.66 (1.17–2.37)	0.005	1.37 (0.93–2.01)	0.115
Drug dealing	3.13 (2.22–4.42)	< 0.001		
Childhood trauma (Moderate/severe vs. none/low)				
Sexual abuse	1.31 (0.85–2.02)	0.220		
Physical abuse	1.35 (0.94–1.94)	0.108		
Emotional abuse	1.31 (0.92–1.88)	0.131		
Physical neglect	1.54 (1.09–2.19)	0.015	1.51 (1.06–2.15)	0.023
Emotional neglect	1.34 (0.93–1.91)	0.112		

CI: confidence interval; DTES: Downtown Eastside; NMPO: Non-medical prescription opioids.
[a] Yes vs. no, except for age and childhood trauma-related variables.
[b] Variables were selected using a confounding model building approach with backwards selection process.
[c] Self-identified (used reported gender identity at latest study visit).
[d] Refers to exposure in last 6 months.
[e] All substance use variables were time-updated and lagged to the prior study visit to protect against reverse causation.

Table 4
Unadjusted and adjusted hazard ratios (HRs) for factors associated with heroin injection initiation, when PO use includes non-injection PO use only, among street-involved youth (n = 652).

		Hazard Ratios (HR)		
Characteristic[a]	Unadjusted HR (95% CI)	*p*-value	Adjusted HR[b] (95% CI)	*p*-value
Sociodemographic factors				
Age (per year older)	0.96 (0.90–1.02)	0.150		
Gender (male vs. female)[c]	1.03 (0.70–1.50)	0.897		
White ethnicity/race (yes vs. no)[c]	1.02 (0.72–1.45)	0.920		
High school completion (yes vs. no)	0.83 (0.59–1.16)	0.265		
DTES residence (yes vs. no)[d]	2.09 (1.49–2.93)	< 0.001	1.69 (1.16–2.47)	0.006
Homelessness (yes vs. no)[d]	2.02 (1.41–2.89)	< 0.001	1.54 (1.03–2.31)	**0.035**
Incarceration (yes vs. no)[d]	1.63 (1.11–2.41)	0.014	1.31 (0.84–2.05)	0.234
Sex work (yes vs. no)[d]	2.55 (1.40–4.65)	0.002	1.49 (0.71–3.11)	0.291
Substance-use related behaviors[d,e] (yes vs. no)				
Non-injection NMPO use	1.68 (1.03–2.74))	0.038	1.21 (0.71–2.05)	0.476
Non-injection heroin use	2.87 (1.96–4.19)	< 0.001	1.93 (1.25–2.97)	**0.003**
Crack cocaine use	1.14 (0.80–1.64)	0.464		
Crystal methamphetamine use	1.56 (1.00–2.43)	0.048	1.99 (1.38–2.88)	< **0.001**
Daily cannabis use	1.17 (0.83–1.64)	0.373		
Heavy alcohol use	0.88 (0.61–1.26)	0.452		
Drug or alcohol treatment	1.87 (1.33–2.63)	< 0.001	1.61 (1.10–2.37)	**0.015**
Drug dealing	1.79 (1.27–2.53)	0.001	1.26 (0.85–1.87)	0.251
Childhood trauma (Moderate/severe vs. none/low)				
Sexual abuse	1.40 (0.93–2.12)	0.106		
Physical abuse	1.40 (0.98–2.01)	0.064		
Emotional abuse	1.09 (0.77–1.54)	0.643		
Physical neglect	1.22 (0.84–1.75)	0.293		
Emotional neglect	1.48 (1.04–2.11)	0.029	1.33 (0.93–1.92)	0.122

CI: confidence interval; DTES: Downtown Eastside; NMPO: Non-medical prescription opioids.
[a] Yes vs. no, except for age and childhood trauma-related variables.
[b] Variables were selected using a confounding model building approach with backwards selection process.
[c] Self-identified (used reported gender identity at latest study visit).
[d] Refers to exposure in last 6 months.
[e] All substance use variables were time-updated and lagged to the prior study visit to protect against reverse causation.

4. Discussion

In the present study, we sought to assess whether NMPO use predicted heroin initiation among street-involved youth who use illegal drugs in Vancouver, Canada. We found that NMPO use was relatively common in this population of street-involved youth, with approximately 1 in 7 reporting NMPO use in the last six months. NMPO use predicted initiation into non-injection heroin use but did not appear to be a significant predictor of heroin injection initiation. However, non-injection heroin use predicted initiation into injection heroin use, suggesting that, for some individuals, non-injection heroin use may act as a pathway between NMPO use and injection heroin use. We found that 15 participants followed the trajectory from non-injection heroin to injection heroin, whereas 10 participants started injection heroin before initiating into non-injection heroin.

Notably, those who used crystal methamphetamines or crack cocaine were over twice as likely to initiate into injection heroin use during the study period compared to those who did not, and the estimated percentages of heroin initiation events attributable to these stimulants were markedly higher than the estimated percentage attributable to NMPO use.

Our results are consistent with prior cross-sectional studies that have identified associations between NMPO use and heroin initiation among youth (Cerdá et al., 2015; Daniulaityte et al., 2009; Lankenau et al., 2012a; Palamar et al., 2016; Peavy et al., 2012; Pollini et al., 2011) and adults (Banerjee et al., 2016; Grau et al., 2007; Martins et al., 2015), as well as another study using data from young people who use NMPOs that found that using non-oral NMPOs (e.g., sniffing/snorting, smoking, injecting) vs. oral NMPOs 'most often' was a significant predictor of initiation into heroin use (Carlson et al., 2016).

A recent study from the same setting as the current study found that heroin use predicted NMPO injection initiation, suggesting a pathway of intensification of opioid dependence as opposed to a substitution effect or trajectory away from heroin use (Lake et al., 2018b). Further, evidence suggests that youth who use NMPOs are less likely to seek treatment relative to youth who use illegal street drugs such as heroin

Table 5
Attributable risks for factors associated with non-injection and injection heroin initiation.

Risk factor	Non-injection heroin (*n* = 526)				Injection heroin initiation (*n* = 652)			
	RR[a]	AR[b]	Pc	PAR%[c]	RR[a]	AR[b]	Pc	PAR%[c]
Non-injection PO	1.86	46%	9%	4%				
Crystal methamphetamine	2.70	63%	42%	26%	1.99	50%	46%	23%
Crack cocaine	2.30	57%	71%	40%				
Non-injection heroin					1.93	48%	20%	10%

RR: Relative Risk; AR: Attributable risk percent; Pc: Proportion of participants with risk factor at baseline; PAR%: Population attributable risk percent.
[a] AHR was used as an estimate of RR.
[b] AR% = (RR–1)/RR.
[c] PAR% = (AR%) x (Pc).

and cocaine (Wu et al., 2011), potentially exacerbating opioid dependence and prompting initiation into heroin use.

The current analysis found that crack cocaine and crystal methamphetamine were far more predictive of heroin initiation than NMPO use was, suggesting that stimulant use is a more prominent risk factor for heroin initiation in this setting. Previous studies using data from the same cohort found crystal methamphetamine to predict initiation into injection drug use (Werb et al., 2013). The cheap and easy access to crystal methamphetamine has been suggested to be a driver in the high rates of usage in this population (Hadland et al., 2012; Russell et al., 2008). While there is little research examining transitions between stimulant and opioid use, the opioid and methamphetamine crises, which were previously considered to be distinct, have been described as overlapping, with many individuals using both drugs (The Lancet, 2018). Opioids may be used by those who use stimulants as a way to manage the side-effects of stimulant substance use, such as insomnia, agitation, anxiety (Harro, 2015). Empirical research in this area is warranted, as well as support for those who may be struggling with the side-effects of stimulants.

Our study has limitations. First, as with other studies of street-involved youth, the ARYS cohort is not a random sample and therefore the findings may not generalize to other street populations. Second, this study included self-reported information, which is susceptible to response biases, including recall bias and socially desirable responding. Further, our measures for NMPO use captures perceived use of diverted pharmaceutical POs, though given the proliferation of illegally manufactured POs that are sometimes made to look like pharmaceutical POs, there is potential for misclassification. It is also possible that our measure of 'heroin' included illicitly manufactured Fentanyl, particularly in the later years of the study. However, we have no reason to suspect that any independent variables, including NMPO use, would be reported differentially according to heroin initiation status. Third, as with any non-randomized study, the association between NMPO use and heroin initiation could be influenced by unmeasured confounders despite adjustment for factors known to be associated with drug use trajectories. Fourth, we used the AHR as an estimate of the relative risk (RR) for attributable risk calculations in order to adjust for confounders. While the HR and RR are often used interchangeably in Cox regression modeling, (Symons and Moore, 2002), the HR consistently exceeds RR when it is greater than 1.0 (typically by around 5%), and so all attributable risk measures may have been slightly overestimated. Fifth, we did not assess for frequency of NMPO, length of NMPO, or opioid dependence, so we were not able to determine these factors had an impact on the observed associations between NMPO use and heroin initiation identified in the current study. Sixth, there was significant overlap between participants in the two analyses. The total sample size was 1178 and the total overlap between the two samples was 452 individuals, suggesting that some of the results reproduced between the two analyses may be driven by the same participants making up the study sample. Seventh, some participants missed follow-ups or were followed up for different periods of time. Because the survey questions ask about heroin use in the last six months only, some participants may have initiated heroin while absent from the study, which would not have been captured during the next follow-up. Additionally, some participants were followed up for shorter amounts of time and thus the likelihood of documenting a transition to heroin use was lower when compared to those who were followed up for the entire 12 years of the study. However, our sensitivity analysis suggests that the differential follow-up times did not impact the findings of the study. Lastly, analysis one (initiation into non-injection heroin use) included participants with a history of injection heroin use, as we had insufficient power to detect associations with non-injection heroin initiation when these participants were excluded. Future research should investigate transitions into non-injection heroin use among individuals who have never used any form of heroin.

5. Conclusions

To our knowledge, this is the first longitudinal study to examine pathways between NMPO use and subsequent initiation into non-injection and injection heroin use in a population of at-risk youth. While our findings support the hypothesis that NMPO use is implicated in transitions to heroin injection, it also suggests that that stimulant use, specifically crack cocaine and crystal methamphetamine, may be a more important predictor of heroin initiation. Those who use stimulants may benefit from additional evidence-based policy and programmatic efforts to reduce transitions into more harmful forms of substance use, particularly heroin injection. Further, the findings from the current study suggest that policies and interventions focused on reducing NMPO use (e.g., curbing inappropriate prescribing) may have had limited impact on preventing heroin initiation within this setting and among this unique population. Some studies have suggested that these policies have led to increases in heroin use and overdose (Compton et al., 2016), highlighting the need to increase access to harm reduction services. Future research should continue to explore how safe drug supplies can be provided for those who already use opiates, as well as characterize opioid use transitions among populations of youth, including the impact of frequency and length of use.

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Contributors

Each author has contributed significantly to the work and agrees to the submission. All authors have read and approve the final manuscript.

Declaration of Competing Interest

No conflict declared.

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