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Young adults' opioid use trajectories: From nonmedical prescription opioid use to heroin, drug injection, drug treatment and overdose

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Abstract

Introduction: Recent research has begun to explore the transition from nonmedical use of prescription opioids (POs) to heroin and injection drug use, adding to earlier literature identifying factors that influence the transition from intranasal to injection use of heroin. However, little research has explored how these transitions are embedded within young people's broader opioid use trajectories – individual pathways that may also include experiences of nonfatal overdose and drug treatment.

Methods: Data are from a study of 539 18–29 year-old New York City residents, recruited via Respondent-Driven Sampling, who reported past-month nonmedical use of POs and/or heroin use. Participants completed structured, computer-assisted interviews that included assessment of their ages at a series of “benchmark” events and experiences, including first use of a drug or route of administration, the onset of “regular” use of a drug (i.e., 1 or more times a week for at least 1 month), first overdose and first drug treatment.

Results: Results suggest a predictable, ordered pathway by which opioid use tends to progress in this cohort of young adults. Participants initiated nonmedical PO use at age 16.8, on average, and most transitioned to heroin use (83%) and heroin injection (64%), generally within 4 years of first PO misuse. Drug treatment was not typically accessed until after participants had progressed to heroin use. First overdose occurred < 1 year after first heroin use, on average.

Conclusions: Findings may help inform the optimal timing for delivery of primary, secondary and tertiary prevention efforts targeting young opioid users.

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Contributors

Pedro Mateu-Gelabert and Honorio Guarino designed the study. Jennifer Teubl conducted the statistical analyses. Elizabeth Goodbody contributed to the data collection, as well as initial literature searches. All authors contributed substantively to the interpretation of the data and the findings. Honorio Guarino wrote the manuscript and all authors have approved the final manuscript.

Conflict of interest

None of the authors have conflicts of interest to declare.

Keywords

Nonmedical prescription opioid use; Heroin; Injection drug use; Young adults; Drug transitions; Opioid use trajectories

1. Introduction

After increasing dramatically since the late 1990's, national rates of the nonmedical use of prescription opioids (POs) and PO-associated overdose fatalities have begun to decrease in the face of intensifying concern about the country's opioid epidemic and overdose crisis and the institution of new medical, regulatory and law enforcement measures intended to curb inappropriate prescribing and illicit diversion of opioid-based pharmaceuticals. Yet the opioid epidemic has continued to expand, driven by recent increases in heroin use and heroin-related overdose deaths. From 2010 to 2015, the percentage of overdose deaths involving heroin tripled from 8% to 25% nationwide, while in the same period, overdose deaths involving opioid analgesics decreased from 29% to 24% (Hedegaard, Warner, & Miniño, 2017). Parallel trends have occurred in New York City, the location of the present study. In 2016, heroin was involved in 55% of all fatal overdoses, while POs were involved in only 18% (Paone, Nolan, Tuazon, & Blachman-Forshay, 2017). Young adults are a key population affected by these trends; their rates of opioid misuse are especially high, and emerging adulthood is a critical period for the development of substance use patterns that can endure well into adulthood. Over the past decade, 18–25 year-olds had the highest rate of heroin use of any age group, with their rate of heroin use more than doubling during this period (CDC, 2015).

1.1. Previous research on opioid use transitions and trajectories

A number of observers have posited a causal relationship between decreases in PO misuse and increases in heroin use, in light of evidence indicating that a majority of today's new heroin users, in contrast to earlier generations of heroin users, initiated opioid use with the non-medical use of POs and subsequently transitioned to heroin, motivated by heroin's cheaper cost and greater accessibility (Cicero, Ellis, Surratt, Kurtz, 2014; Jones, 2013; Muhuri, Gfroerer, & Davies, 2013). Although the proportion of nonmedical PO users who ultimately transition to heroin use appears to be small (Compton, Jones, & Baldwin, 2016), the existence of this phenomenon among geographically diverse groups of opioid users in the U.S. is now well-established (Cicero et al., 2014; Muhuri et al., 2013), and the CDC recognizes PO misuse as the single greatest risk factor for heroin use (CDC, 2015).

Transition to heroin has in turn been closely linked to the uptake of injection drug use (Liebling, Green, Hadland, & Marshall, 2017; O'Keefe, Horyniak, & Dietze, 2016), a behavior that significantly increases young people's vulnerability to HCV, HIV and other health-related harms.

Emerging research has begun to explore risk factors associated with transitions from PO misuse to heroin use, adding to a body of earlier work on the transition from intranasal to injection use of heroin. To date, most studies conducted with young nonmedical PO users have identified a limited range of drug-related predictors of progression to heroin that are

indicative of greater-severity use, such as earlier onset and higher frequency PO misuse and co-occurring use of other drugs (Carlson, Nahhas, Martins, & Daniulaityte, 2016; Cerda, Santaella, Marshall, Kim, & Martins, 2015; Palamar, Shearston, Dawson, Mateu-Gelabert, & Ompad, 2016; Surratt et al., 2017). On the social network level, having peers and sex partners who inject has long been re-cognized as a critical factor preconditioning injection initiation, through mechanisms including exposure to injection, the influence of initiators and group norms accepting of injection (Harocopoes, Goldsamt, Kobrak, Jost, & Clatts, 2009; Neaigus et al., 2006; Sherman, Smith, Laney, & Strathdee, 2002). Psychosocial and structural factors found to be associated with transition to injection include childhood trauma, homelessness and other indices of social dislocation and dis-advantage (Abelson et al., 2006; De Beck et al., 2013; Fast, Small, Krusi, Wood, & Kerr, 2010).

1.2. The present study

An under-explored area concerns how young people's transitions from nonmedical PO use to heroin and injection drug use are embedded within their broader opioid use trajectories – individual pathways that may include the misuse of other prescription and non-prescription drugs, as well as one or more non-fatal overdoses and drug treatment episodes. To begin to address this gap, the present study provides a more holistic and fine-grained understanding of the opioid use trajectories of young adults who began using opioids when POs were widely available.

Using data from a sample of 539 New York City young adults (ages 18–29) who reported past-month nonmedical PO use and/or heroin use, we characterize youths' opioid use trajectories by identifying a series of common milestones or “benchmarks”. Based on the mean ages at which participants progressed to each benchmark, we propose a sequential model of opioid-related transitions that underlies the experience of a majority of participants. The study aims to advance existing research on young people's opioid use trajectories in several ways. To expand a trajectory model beyond transitions from nonmedical PO use to heroin and injection drug use, we consider their temporal relationship to key events including youths' first experience of opioid-related overdose and first entry into treatment for opioid use disorder (OUD). To better understand how youths' opioid use escalates, we distinguish between first use of a drug and the onset of regular use, an aspect of trajectory re-search that has received relatively little attention. Finally, given the commonality of polydrug and poly-pharmaceutical use in the new generation of opioid users – in particular, the co-occurring nonmedical use of benzodiazepines and opioids (Calvo et al., 2017; Mateu-Gelabert et al., 2017) – we consider the location of benzodiazepine misuse within the overall sequence of transitions. Study findings may have important implications for the development and dissemination of tailored drug prevention, treatment and harm reduction services for opioid-using youth – for example, by helping to inform the optimal timing for delivering primary and secondary prevention interventions.

2. Methods

2.1. Design and sample

This study is based on data collected in 2014–2016 from 539 opioid-using young adults in New York City for a cross-sectional study of opioid use patterns and risk behaviors. Detailed information about the study's methodology has been previously published (Mateu-Gelabert et al., 2017). Participants were recruited by Respondent-Driven Sampling (RDS), a form of chain-referral sampling designed to engage hard-to-reach populations that uses participants' social network connections to drive recruitment. In this process, 20 eligible individuals were directly recruited by research staff to initiate recruitment chains, with the remainder of the sample recruited by means of peer referrals from previous participants. Eligible participants: were 18–29 years old; lived in New York City; reported nonmedical use of POs and/or heroin 3 or more times in the past 30 days; and spoke English. Structured, computer-assisted interviews assessed participants' socio-demographics, opioid use trajectories, overdose experiences and drug treatment histories. HCV status was assessed by on-site rapid antibody testing (Or-aSure Technologies). The study was approved by NDRI's Institutional Review Board, and all participants provided written informed consent.

2.2. Measures and variable definitions

We conceptualize trajectory “benchmarks” as key turning points in an individual's drug use career. Benchmarks assessed in this study include: the initiation of distinct drug use behaviors, such as first use of a drug/drug class (e.g., first nonmedical PO use, first heroin use) or route of administration (e.g., first heroin injection); the onset of regular use of a drug/route of administration; and drug-related events or experiences (i.e., first overdose, first OUD treatment). For each benchmark (presented in Table 2), participants were asked a variant of the question, “How old were you when you [e.g., first used heroin on a regular basis]?” Responses were measured in years and recorded as whole numbers. For all benchmark behaviors, “regular” use was defined as “one or more times a week for at least one month.”

In the absence of a standardized definition of opioid-related over-dose, we adopted a fairly stringent definition to minimize ambiguity and over-reporting. Participants were advised to consider an event an overdose if they “lost consciousness, stopped breathing and/or required emergency assistance (e.g., use of naloxone, intervention of emergency personnel).”

2.3. Data analysis

All analyses were conducted in the program R, versions 3.2.2 and 3.2.4 (R Core Team, 2015). Descriptive statistics, including frequencies, standard deviations, 95% confidence intervals and mean and median ages, were prepared for all benchmark behaviors and events, as well as supplementary variables relating to key transitions. RDS population estimates were calculated for sociodemographic variables using the successive sample estimator (Gile, 2011) in the R package RDS (Handcock, Fellows, & Gile, 2012). This technique generates prevalence estimates for a sample's target population by accounting for the dependence within an RDS sample (as participants are recruited by other participants), as well as other potential sources of recruitment bias. Because RDS population estimates could not be

generated for means and medians, we opted not to report these estimates for any drug-related variables. To assess the significance of differences in the mean ages at which participants reported initiating benchmark behaviors and events, we conducted a series of two-tailed paired t-tests with successive pairs of variables.

3. Results

3.1. Socio-demographics

Participants' socio-demographic characteristics, along with RDS population estimates for the target population of opioid-using 18–29 year-olds in New York City, are presented in Table 1. It is notable that these population estimates are generally close in value to the sample frequencies – within one to two percentage points for most variables – which suggests that the sample may be fairly representative of opioid-using young adults living in New York City.

3.2. Overview of young adults' opioid use trajectories

A generalized trajectory model, representing the opioid use transitions of the majority of participants, is presented in Table 2. Overall, the series of benchmark behaviors and events increases in severity as the age at which participants initiated them increases, over a nearly 4-year timespan, from initiation of nonmedical PO use at the mean age of 16.8 to first PO injection at the mean age of 20.6. At the same time, the proportion of youth who progressed to each successive benchmark generally decreases, although a strong majority transitioned to the key milestones of heroin use (83%), almost 3 years on average after initiating PO misuse, and heroin injection (64%), less than one year after first heroin use. In virtually all instances, t-test results (Table 3) show significant differences in the mean ages at which participants reached different benchmarks, suggesting a common sequence of transitions across participants.

3.3. Key transitions in the progression of young adults' opioid use

To provide context for the trajectory model in Table 2, this section reports additional descriptive data regarding salient transition points in the progression of participants' opioid use.

3.3.1. Initiation of nonmedical prescription opioid use—Initiation of nonmedical PO use typically involved immediate-re-lease oxycodone (54%) or hydrocodone (27%) obtained for free from friends, relatives or household sources and ingested orally (80%). First experiences with PO misuse typically occurred in a social setting with peers, and the most frequently endorsed motivations for initiation were to get high (90%), to satisfy curiosity (78%), and to party and hang out with friends (50%).

Results suggest that, while iatrogenic initiation of PO use may have occurred in a minority of youth, nonmedical initiation was the dominant pattern. Although 71% of the sample had ever been prescribed POs for pain, only 13% reported receiving their first prescription before initiating nonmedical use. (An additional 11% received their first PO prescription during the same age-year they began nonmedical use.)

3.3.2. Transitions to injection drug use—On average, participants initiated heroin injection (at the mean age of 20.4) less than one year after first using heroin (at the mean age of 19.6), typically by the intranasal route. Participants also tended to begin injecting heroin shortly after their heroin use had progressed to a regular behavior (at the mean age of 20.3).

Whereas heroin injection was reported by a majority of participants (64%), only a little over one-third (37%) reported ever injecting POs, and a small minority (16%) engaged in PO injection on a regular basis. Further, most participants who injected POs first did so after they had already injected heroin. The seemingly counter-intuitive result whereby the mean age at initiation of regular PO injection (20) is younger than the mean age at first PO injection (20.6) is an effect of the small subset who reported regular PO injection. Because this sub-group had accelerated trajectories characterized by significantly earlier onset of most benchmark behaviors, including PO injection, they progressed to regular PO injection well before other participants first experimented with this behavior.

3.3.3. First overdose—A sizeable minority (43%) reported lifetime overdose experience. First overdose (mean age = 20.2) tended to occur after the uptake of heroin use and before the onset of regular heroin use and heroin injection. Among those who had ever overdosed, 59% had a history of multiple overdoses, with a mean of 4.9 lifetime overdoses (SD = 4.72).

3.3.4. First drug treatment—Although a significant majority (70%) reported a history of drug treatment, treatment was not typically accessed until age 19.8, on average – about 3 years after initiation of nonmedical PO use, 1½ years after progression to regular PO misuse and 5 months after first heroin use. Among those who had ever been in drug treatment, a broad range of modalities was represented, with approximately 30% of participants, respectively, reporting current or prior enrollment in either buprenorphine or methadone maintenance treatment.

4. Discussion

Taken together, these findings suggest that, for many of today's young opioid users, the initiation of nonmedical PO use in mid-adolescence provided the entryway into long-term opioid use. A defining feature of participants' opioid use trajectories is escalation to increasingly severe or risky forms of use, including co-occurring benzodiazepine and opioid misuse, heroin use and drug injection. Results further suggest a predictable, ordered pathway by which opioid use tends to progress in this group of youth. Participants reported reaching the benchmarks in our trajectory model at remarkably similar ages, suggesting both a common sequence of transitions and a predictable timeframe for the emergence of distinct opioid use-related behaviors. Nevertheless, it is also important to emphasize a countervailing feature of this trajectory: the prevalence of the benchmark behaviors and events decreases as the pathway progresses. A varying proportion of participants who initiated nonmedical PO use did not progress to each subsequent benchmark in the trajectory, illustrating that escalation of opioid use is not uniform or inevitable for this group of youth.

While aspects of this trajectory model resemble the classic Stage Model of Substance Use (Catalano, White, Fleming, & Haggerty, 2011), there are critical distinctions. Most saliently, we do not posit the universality of this trajectory, but understand it as specific to a cohort of young people who came of age in a particular socio-historical context when rates of medical and nonmedical PO use were reaching un-precedented levels in the U.S. The extent to which this model may apply to future generations of young drug users remains to be seen. Moreover, whereas the classic Stage Model recognizes variation chiefly in terms of how far along a unidirectional pathway of escalating substance use an individual does or does not progress, we believe it is important to emphasize that, at each stage in the generalized pathway we describe, there are a range of exceptions to the dominant pattern.

Although the majority of the sample is White and male, as is typical of the new generation of opioid-using youth (Cicero et al., 2014; Jones, 2013), Hispanics/Latinos, women and various socioeconomic strata are well-represented. This diversity suggests that the trajectory we describe is not limited to a narrow subset of opioid-using young adults. Because participants were recruited through peer-based social networks using RDS, the sample is distinctive from many recent studies of opioid-using youth that are based on samples of drug treatment or harm reduction clients or street-based, homeless youth (Cicero, Lynskey, Todorov, Inciardi, & Surratt, 2008; Lankenau et al., 2012; Calvo et al., 2017). The use of RDS, a methodology specifically designed for sampling “hidden” populations, may have allowed us to reach less visible members of the target population, such as those not engaged with drug-related services or those with less frequent opioid use, potentially increasing the generalizability of the findings.

With regard to the timing of transitions to heroin use and drug injection, our results both support and extend previous research. For example, Cerda et al.’s (2015) analysis of national data identifies ages 17–18 as the peak period for heroin initiation among youth with histories of nonmedical PO use, while Carlson et al.’s (2016) longitudinal study of initially non-opioid dependent PO users in Ohio reports a mean age of 22 at first heroin use. These results are broadly consistent with present findings indicating a median age of 19 at heroin initiation. Regarding age at onset of injection drug use, studies of young injectors have reported somewhat earlier ages at first injection (e.g., 17–18 versus our sample’s median age of 20 at first heroin injection; Lankenau et al., 2012; O’Keefe et al., 2016), which may reflect the relative diversity of our sample in terms of injection status and socio-demographic characteristics.

The finding that participants who reported (non-regular) PO injection did not typically initiate the behavior until after being initiated into injection via heroin may relate, at least in part, to the mechanics of PO injection. Relative to injecting heroin (especially the powdered heroin available in New York City), breaking down opioid-based pills into an injectable solution is a cumbersome and time-consuming process (Mateu-Gelabert, Guarino, Jessell, & Teper, 2015; Roy, Arruda, & Bourgois, 2011). This may help explain why heroin injection became a normative behavior for many participants, but regular PO injection was practiced by only a small subset whose accelerated trajectories may indicate greater entrenchment in a drug scene. The low prevalence of PO injection is also likely a function of geographic and socio-structural factors, including New York City’s long-standing and robust heroin market.

Studies conducted with opioid users in rural locations without established heroin markets (Young & Havens, 2011; Zibbell, Hart-Molloy, Barry, Fan, & Flanigan, 2014) have found significantly higher rates of PO injection.

On the whole, the results of this study highlight a need for innovative behavioral, community-level and structural interventions to prevent, delay or attenuate the escalation of opioid use in young people. These findings may help inform the optimal timing for delivery of primary and secondary prevention interventions to vulnerable groups of youth. For example, to prevent initiation of PO misuse, primary prevention efforts should ideally target pre-adolescents. Similarly, in light of participants' brief period of heroin sniffing, interventions to prevent injection uptake may find it fruitful to target nonmedical PO users who have not progressed to regular heroin use, as well as regular heroin users.

Results also indicate a need for expansion of evidence-based OUD treatment, particularly maintenance treatment with methadone and buprenorphine, as well as new treatment delivery models for young opioid users. This is suggested by the high proportion of participants who reported progressing to regular heroin use and heroin injection, as well as the finding that most did not access drug treatment until after they had progressed to heroin use, at which point, they had been misusing POs for 3 years, on average, and doing so on a regular basis for 1½ years. Low-threshold, non-judgmental and readily accessible delivery models may help engage youth in effective, evidence-based treatment earlier in the course of their opioid use trajectories before they progress to riskier forms of use, such as injection drug use, that increase their vulnerability to serious health-related harms. Youth-focused and harm reduction-informed MAT models that accommodate young people's specific needs and preferences, such as treatment-on-demand, MAT that is not conditional on total abstinence and programs for couples, may be appealing to this population. Additionally, expanded use of effective psychosocial and behavioral treatment modalities (e.g., evidence-based family therapy for youth who maintain relationships with their families, self-management modalities such as cognitive behavior therapy or mindfulness training) could enhance outcomes for young adults in MAT, particularly those also misusing benzodiazepines or other drugs, and provide options for those who prefer non-medication-based treatment.

The finding that participants' first overdose tended to occur < 6 months after their first episode of drug treatment suggests that treatment programs have a critical role to play in expanding access to overdose prevention/reversal education and naloxone (especially since the period immediately after leaving drug treatment is a well-known time of heightened risk for overdose). Finally, targeted outreach efforts to engage the new generation of young opioid users (including those who inject, as well as those who have not transitioned to regular injection) should be developed to involve them in harm reduction programs, inform them of the HCV/HIV and other risks associated with drug injection, provide OD prevention/response training with naloxone, and reduce stigma associated with services such as syringe exchange and methadone maintenance which can be high in this group (Frank et al., 2015; Gunn & Guarino, 2016).

4.1. Limitations

The study's most salient limitation relates to the cross-sectional design and use of retrospective, self-reported data. Participants' ability to accurately recall their opioid use histories, including behaviors and events that may have occurred a number of years in the past, is unknown. However, such designs are common in national-level and community-based studies of drug users (Calvo et al., 2017; Cerda et al., 2015; O'Keefe et al., 2016). Because the sample consists entirely of New York City residents, results may not generalize to young opioid users in other areas, particularly rural locations. The use of a non-random re-cruitment method, RDS, may also have introduced bias into the sample that limits the generalizability of the findings. Other limitations relate to the measurement of certain variables. For participants who reported reaching two or more benchmarks at the same age, we were unable to determine the sequence of these events which may have reduced the precision of our trajectory model. The study's assessment did not include screening for OUD diagnosis per DSM-V criteria or ask participants the modality of their first drug treatment (including whether it involved MAT), information which may have helped refine our understanding of young adults' opioid use trajectories. In view of these limitations, the findings should be considered preliminary and are intended to provide a foundation for future research.

Longitudinal research (which our team hopes to conduct) is necessary to confirm and elaborate this trajectory model and assess its applicability to future cohorts of opioid-using youth. Prospective cohort studies may also be useful in developing a typology of opioid use trajectories, including arrested and accelerated pathways, and associated multi-level predictors. The identification of modifiable protective factors could have direct relevance for the development of innovative primary and secondary prevention interventions, as well as tailored treatment and harm reduction models, to help change the course of young people's opioid use trajectories.

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HIGHLIGHTS

- Youth began PO misuse at age 16.8 on average; 86% progressed to regular PO misuse.
- 92% of opioid-using youth had also misused benzodiazepines; 56% did so regularly.
- Most PO users transitioned to regular heroin use (79%) and heroin injection (64%).
- Regular heroin use and heroin injection began about 3½ years after first PO misuse.
- First OD occurred at the mean age of 20.2, < 1 year after first heroin use.

Table 1

Socio-demographic characteristics of young adult opioid users in New York City, 2014–16, n = 539.

Characteristic	Sample prevalence%	RDS population estimate % (standard error)
Age (years)	M = 24.5 (SD = 3.1)	–
Gender		
Male	68 ^a	70 (4.1)
Female	32	30 (4.1)
Transgender	1	1 (0.3)
Ethnicity		
Hispanic/Latino	29	30 (4.3)
Race		
White	69	68 (4.6)
Black/African-American	8	9 (3.3)
Multiracial	8	6 (1.6)
American Indian or Alaskan Native	2	2 (1.0)
Asian	1	1 (0.7)
Did not respond ^b	12	14 (3.9)
Household Income Growing Up (annual)		
< \$50,000	42	43 (4.7)
\$51,000–100,000	33	33 (4.0)
\$101,000 or more	19	17 (2.7)
Homeless/unstably housed		
Ever	57	61 (4.9)
Currently	25	30 (4.2)
Hepatitis C-positive	20	20 (3.6)

^aPercentages may total over 100 due to rounding.^bMissing race data is largely due to Hispanic/Latino participants reporting ethnicity, but not race.

Table 2

Benchmark behaviors and events in participants' opioid use trajectories: frequencies and ages at initiation

	1st nonmedical PO ^a use	1st nonmedical BZD ^c use	1st regular PO use ^d	1st regular BZD use	1st heroin use	1st drug Tx	1st regular PO injection	1st overdose	1st regular heroin use	1st heroin injection	1st PO injection
N	531 ^b	496	465	303	445	377	87	234	423	345	197
%	99%	92%	86%	56%	83%	70%	16%	43%	79%	64%	37%
Mean Age	16.8	17.9	18.3	18.8	19.6	19.8	20	20.2	20.3	20.4	20.6
SD	3.1	3.3	3.1	3.4	3.6	3.6	3.6	3.8	3.4	3.7	3.6
95% CI	16.5–17.1	17.6–18.2	18–18.6	18.4–19.2	19.3–19.9	19.4–20.2	19.2–20.8	19.7–20.7	20–20.6	20–20.8	20.1–21.1
Median Age	17	17	18	18	19	19	20	21	20	20	20

^aPO = prescription opioid.

^bOf the total sample size of 539, 6 participants reported never initiating nonmedical PO use and 2 participants did not report their age at first nonmedical PO use.

^c. BZD = benzodiazepine.

^dFor all behaviors, "regular" use is defined as one or more times per week for at least one month.

Table 3

Results of paired t-tests on participants' mean ages at initiating benchmark behaviors and events, p-values.

	1st nonmedical PO use ^a	1st nonmedical BZD ^b use	1st regular PO use	1st regular BZD use	1st heroin use	1st drug Tx	1st regular PO injection	1st overdose	1st regular heroin use	1st heroin injection	1st PO injection
1st nonmedical PO use											
1st nonmedical BZD use	< 0.0001 ^c										
1st regular PO use	< 0.0001	0.001									
1st regular BZD use	< 0.0001	< 0.0001	< 0.0001								
1st heroin use	< 0.0001	< 0.0001	< 0.0001	0.018							
1st drug treatment	< 0.0001	< 0.0001	< 0.0001	0.002	0.083						
1st regular PO injection	< 0.0001	< 0.0001	< 0.0001	0.026	< 0.0001	0.004					
1st overdose	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	0.364				
1st regular heroin use	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	0.039	0.001	0.001			
1st heroin injection	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	0.019	0.001	< 0.0001	0.001		
1st PO injection	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	0.001	< 0.0001	0.442	< 0.0001	< 0.0001	< 0.0001

^aPO = prescription opioid.^bBZD = benzodiazepine.^cp-values < 0.05 are considered significant and indicated in bold.