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Hcv And Drug Transition In Ct Nonurban Injection Drug Users

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Abstract

Aims: We sought to determine if age of first substance initiation (alcohol intoxication, marijuana use, pharmaceutical opioid use, polysubstance) was associated with faster rates of transition to injection drug use or heroin use. Subsequently, we examined if transition time was a predictor for hepatitis C infection.

Methods: From 2008-2012, 462 active injection drug users were recruited using respondent-driven sampling. Participants were interviewed about their injection-associated risk, and serological testing of HIV, HCV and HBV was performed. Kaplan-Meier analyses were used to examine the rate of transition from first substance event to initiation of heroin use or first injection. A Cox proportional hazards regression model was used to examine risk of transition, and regression analysis was performed to assess transition time as a predictor of HCV infection.

Results: Age of initiation was categorized into young and old based on the median age of the specific substance. Individuals initiating alcohol intoxication, marijuana use, and polysubstance use at older ages had faster transitions to both heroin and injection drug use. Younger pharmaceutical opioid initiates did not have significantly different transition times than older initiates, although the risk of early transition to heroin (AHR=1.7; 95% CI=1.3-2.3) and injection drugs (AHR=2.3; 95% CI=1.7-3.2) was significantly greater in older initiates. The adjusted odds of HCV infection decreased with increasing transition times to injection from initiation of opioid use by 9%, of polysubstance use by 13%, of marijuana use by 9%, and of alcohol intoxication by 8%.

Conclusions: Older initiates of pharmaceutical opioids, alcohol intoxication, and marijuana use are at greater risk of early transition to heroin use and injection of any drug than younger initiates, but initiate heroin use and injection at similar ages. Effective prevention strategies aimed at delaying transition to heroin use and injection drug use, particularly in older initiates, are needed to prevent incident HCV infections in this nonurban injection drug user population.

Table of Contents

List of Tables and Figures

1. Background

In the United States, injection drug use continues to be a major risk factor for blood-borne infections such as HIV, hepatitis B (HBV), and hepatitis C (HCV) [1]. Illicit drug use is increasingly common, as nearly 9% of the non-institutionalized population 12 years old and older reported usage of illicit drugs in the previous month to data collection, in the 2009 National Survey on Drug Use and Health. In the same survey, approximately 425,000 people from 2006-2008 reported injection drug use (IDU) of either heroin, cocaine, or stimulants in the year preceding data collection. [1]. Engaging in risky sexual behavior and risky injection practices such as sharing unsterile drug injection equipment can facilitate the transmission of blood-borne infections [1, 2]. In 2012, nearly 50% of new HCV infections in the United States were associated with injection drug use, making the need for adequate prevention methods essential for reducing HCV transmission [1].

What was once considered to be a problem exclusive to large urban centers has now become a recognizable problem in nonurban areas too [3]. The Monitoring the Future data from 1976 to 1992 showed that in some years, rural areas had a greater prevalence of illicit drug use than urban areas and vice versa in other years [3]. Between 2007 and 2010, the National Survey of Drug Use and Health Use found a 10-15% increase in the percentage of people injecting drugs in smaller metropolitan and suburban communities [4]. Research by Cicero *et al*. (2007) found that opioid abuse was higher in smaller urban, suburban, and rural areas compared to the medically prescribed opioid use in the same area [5]. Urban and non-urban areas can differ on a large variety of factors such as income, population density, the built environment, drug availability, transportation availability, and availability of health services and treatment centers [3]. Therefore, it is unlikely that drug user populations in urban areas are comparable to users in suburban and rural settings. Despite the increases in illicit drug use in suburban and rural settings over the years, little research has studied the drug user population in nonurban environments. Thorpe *et al*. (2001) compared young suburban and urban injection drug users in Chicago from 1997-1999 and found that suburban people who inject drugs (PWID) engaged in riskier injection practices such as sharing paraphernalia and remained at high risk for blood-borne infections [6]. Heimer *et al*. (2014) have also studied nonurban PWIDs in Southwestern Connecticut and found that those living in economically disadvantaged neighborhoods did not have a greater HIV risk, unlike urban PWID [4]. However, little work has been done in studying the transition of drug use to injection in nonurban populations.

The transition from substance use to injection drug abuse can be studied from two approaches: the drug trajectory of an individual and the initiation age of substance use. The association between drug type used for initiation and progression to injection has long been studied. The gateway hypothesis

proposed by Kandel (1975) suggested drug use follows a pattern of structured escalation where an adolescent who starts using will begin with more socially acceptable drugs and progress to "harder" drugs such as cocaine and heroin [7-10]. Studies have consistently found, with a few exceptions, that adolescents began with alcohol and/or cigarette use before progressing to marijuana and other illicit drugs [7, 8, 11]. In recent years, prescription opioids have become a common drug that preceded initiation into illicit drug injection, and opioid misuse typically followed alcohol, cannabis, and prescription stimulant use [12]. However, the pharmaceutical opioid, OxyContin, was not found to be a gateway drug, but polyopioid drug use within the first year of initiating opioid use was associated with a faster progression to heroin and drug injection abuse [13].

The growing population of young PWID is disconcerting because this population has been found to engage in riskier sexual behaviors and risky injection practices, which increases their risk for HCV and HIV infections [14-17]. The CDC has reported an increase in HCV incidence among 15-24 year olds in Massachusetts and in those less than 30 years old in New York and Wisconsin [17]. HCV infection typically occurs within the first 2 years after initiating injection drug use, thus understanding the mechanisms and behaviors behind transition could impact prevention efforts [15]. Few studies have looked at transition time in nonurban populations and the potential relationship with HCV infection.

This study aims to (a) determine if age of initiating marijuana, pharmaceutical opioids, first intoxication, or polysubstance use (i.e., at least two of alcohol intoxication, marijuana, or pharmaceutical opioid use in the same year) is associated with faster rates of transition to injection and heroin use, and (b) determine if transition time is a risk factor for HCV infection in a nonurban PWID population residing in southwestern Connecticut.

2. Methods

The study was a longitudinal study of PWID who resided in the nonurban towns of Fairfield and New Haven Counties of Connecticut. The Yale Human Investigations Committee approved the study protocol and informed consent process. Information on more detailed methods can be found in published articles [4, 18, 19].

2.1. Study Sample

From November 2008 to Jan 2012, 462 participants were enrolled into the study. Before providing informed consent, participants were required to meet the eligibility criteria of: a) $\geq$ 18 years of age, b) self-reported injection drug use within the prior 30 days, c) proof of residency for at least 6 months in Fairfield or New Haven Counties, excluding the major urban areas of Bridgeport, Danbury, New Haven, Stamford, Norwalk, and Waterbury, d) willingness to be interviewed, answer questions in a survey, and provide blood samples for serological testing as a participant in the longitudinal study, and e) ability to provide informed consent [4, 18, 19]. Participants were recruited through respondent-driven sampling (RDS), a common recruitment strategy used for hidden populations such as PWID [20, 21]. For the RDS, eligible individuals were randomly chosen to be seeds and were given coupons to distribute to people they believed would be eligible for study inclusion [4]. These recruits were in turn given coupons to continue the recruitment process [21]. Social service agencies, substance abuse treatment programs, and advertisements were used as resources for the recruitment of 82 seeds [4, 18, 19].

2.2. Data collection

The two-part baseline quantitative survey completed by study participants consisted of a face-to-face interview with field researchers and a self-administered survey using the Audio-Computer Assisted Self Interview (A-CASI) software (NOVA Research Company, Bethesda, MD). As described in previous publications, the survey collected data on sociodemographics, social support, substance abuse, general medical history, current injection behaviors, clinical screening instruments, HIV, hepatitis and overdose knowledge, interactions with harm reduction programs and the criminal justice systems [4, 18, 19]. Data collected for clinical screening purposes included the Brief Pain Inventory[22, 23], the Addiction Severity Index (ASI)[24-26], Center for Epidemiological Studies Depression Scale (CES-D)[27], the Beck Anxiety Index (BAI)[28, 29] and the Alcohol Use Disorders Identification Test (AUDIT-C) [4, 18, 19, 30, 31]. In addition to the completion of the baseline survey, participants provided a 4-6 mL blood sample for serological testing for HIV, HCV and HBV. Blood was drawn by a trained phlebotomist, from which serum was prepared and stored at -20°C until testing with serological test kits occurred (Bio-Rad Laboratories, Hercules, CA)[4]. Individuals who tested positive for any test were informed in a face-to-face meeting and referred to services that could provide confirmatory testing [4, 18, 19]. Counseling on how to prevent transmission was also provided at this meeting [4, 18, 19]. Individuals who tested negative were told they were susceptible and counseled to receive vaccination [4, 18, 19].

2.3. Variables

2.3.1. Any drug and polysubstance variables

The drug injection variable refers to the youngest age of injection of at least one of the following drugs: heroin, methadone, buprenorphine, pharmaceutical opioid, crack, cocaine, methamphetamine, non-prescribed stimulant, or non-prescribed sedatives or barbiturates. The polysubstance variable is limited to individuals with at least two first substance use exposures–alcohol intoxication, marijuana use or pharmaceutical opioid use–in the same year.

2.3.2. Transition time variable

Heroin transition time in this study refers to the time between reported age of first substance event (first alcohol intoxication, first marijuana use, first pharmaceutical opioid use, or polysubstance use) and reported age of first heroin use in any form. The injection transition time refers to the time between reported age of first substance event (first alcohol intoxication, first marijuana use, first pharmaceutical opioid use, and polysubstance use) and reported age of first injection of any drug.

2.3.3. Survival Analysis variables

The age of first intoxication, first marijuana use, and first pharmaceutical opioid use were dichotomized into younger initiates and older initiates based on the median age for each substance use. Young initiates include ages below and at the median age, whereas older initiates include ages above the median. The polysubstance variable was dichotomized in the same way.

2.4 Data Analysis

Descriptive statistics for gender, race, education, employment status at time of interview, health insurance status, monthly income, resident town income status, history of arrest, history of being jailed, and HBV and HIV status at time of interview, were analyzed as categorical variables to describe the sample. The study population had few non-white or Hispanic individuals, thus races and ethnicities were grouped together to create a dichotomous categorical variable to compare white Non-Hispanic individuals to all others. Age at the time of interview was analyzed as a continuous variable. Differences in sociodemographics between HCV-positive and HCV-negative individuals were assessed using the Chi-square test (χ^2) or Fisher's test when sample sizes were less than five. For the continuous age variable, the mean difference was compared using the Student's t-test. P-values were considered statistically significant at an alpha level of 0.05. The mean age of first heroin use and first injection for young and old initiates of the first substance event were compared using the Student's independent t-test (α=0.05).

Kaplan-Meier analysis was used to examine the rates of transition from first substance event (alcohol intoxication, first marijuana use, first pharmaceutical opioid use, and polysubstance use) to initiation of heroin use or to first injection of any drug, where the outcome of interest was transition time (years). Those who had never used heroin were right-censored. Study participants who had their first alcohol intoxication or first marijuana use at an age less than or equal to 5 years and those who had their first pharmaceutical opioid, heroin, or injection drug use at an age less than or equal to 9 years were excluded because it could not be determined if these were data entry errors. Finally, participants who reported heroin use or injection drug use at an age prior to their first intoxication, first marijuana, or first pharmaceutical opioid were also excluded.

To ensure temporality assumptions could be made, only characteristics that definitively could have occurred prior to first substance event were included in the Cox proportional model analyses [20]. These characteristics included gender, education, and race. Age at time of interview was also adjusted for because there may have been generational differences between individuals of various ages. The proportional hazards assumption was evaluated for the demographic variables by assessing their interaction with time; age at time of interview was determined to be the only time-dependent variable [32]. To analyze the factors associated with transition rate from initiation of first substance to heroin use or injection drug use, crude hazard ratios and 95% confidence intervals were reported. Adjusted hazard ratios were adjusted for age at time of interview, gender, education level, and race.

To perform a logistic regression to determine if transition time was a predictor for HCV infection, bivariate analyses were conducted using variables such as: sex, race, education, insurance type, town of residence income level, ever jailed, HBV status, age of initiation on substance, age at time of interview, and monthly income level. The backward elimination method was used to derive the most parsimonious model. The likelihood ratio test was used to determine if removal of a variable adversely affected the model fit. Variables that achieved an alpha-level less than 0.05 were retained for considered inclusion in the multivariable logistic regression that was constructed using this backward elimination method. The transition time from first alcohol intoxication, first marijuana use, first pharmaceutical opioid use and polysubstance use to injection drug use were assessed as predictors for HCV status. All analyses were conducted using SAS version 9.4.

3. Results

3.1 Demographics

From 2008 to 2012, 462 eligible participants were enrolled into the study. The mean age of the study population was 35.3 years old (SD: 10.9), and most participants were male (62.3%), white (83.6%), unemployed (71.1%) at the time of study, had government health insurance (66.9%), had been arrested before (89.7%), had been jailed before (71.6%), or were HBV-positive (75.6%) or HIV-negative (98.4%). The majority of participants had completed at least a high school degree (42.2%) or more (39.0%), resided in a town above the median state income (52.2%), but earned less than $1000 per month (53.4%). We compared the demographics of the HCV-positive and -negative individuals (Table 1). HCV-positive individuals were significantly older than HCV-negative individuals ($p<0.001$). There was a statistically significant association between HCV status and type of health insurance, arrest and jail history, and HBV status ($p<0.05$). More than half of the study participants reported initiating injection with heroin (51.1%), but nearly 30% reported initiating injection with two to three different types of drugs in the same year (Table 2).

3.2 Initiation age associated with faster transition rates

To determine if the age of substance initiation was associated with faster rates of transition to injection or heroin use, Kaplan Meier analyses were performed (Table 4). The median transition time from first alcohol intoxication to heroin use was minimally shorter for older initiates than younger initiates, and younger initiates had a significantly slower transition rate to injection (Figure 2). Despite similar transition rates between younger and older initiates, the younger intoxication initiates began using heroin at a significantly younger age than older initiates ($p=0.04$), but not at a significantly younger age for injecting drugs ($p=0.08$) (Table 3). Marijuana use also followed the same pattern, where the median transition time to heroin use was significantly different between younger and older marijuana initiates ($p=0.02$), with older initiates experiencing a faster transition rate but initiating heroin at an overall older age (24.8 years old). The median age of opioid initiation was 18 years old, compared to the median age at first alcohol intoxication or first marijuana use, which were 14 and 13 years old, respectively. Regardless of age of first opioid use, the transition rate to heroin use was not significantly different between younger and older opioid initiates ($p=0.52$), despite the fact that younger initiates began using heroin at a significantly younger age than older opioid initiates ($p<0.001$). The transition rate to injection drug use was significantly different between younger and older opioid initiates ($p=0.04$). Individuals who began using at least two substances within the same year before the age of 14 had a slower transition rate to injection ($p=0.02$) than individuals who initiated polysubstances after the age of 14.

The adjusted hazards ratio of early transition to heroin use or injection use for older initiates was estimated using two Cox proportional hazard regressions (Table 5). Overall, there was an elevated risk of early heroin transition among older substance initiates compared to younger initiates and an elevated risk of early injection transition among older substance initiates too. Relative to younger marijuana initiates, older initiates had a statistically significant increased risk of early transition to heroin use (AHR=1.5; 95% CI: 1.2-1.8) and injection use (AHR=1.9; 95% CI: 1.3-2.6) after adjusting for age, race, gender and education. Similarly, compared to younger pharmaceutical opioid initiates, older initiates had a significant increase in risk for transitioning more quickly to heroin use (AHR=1.7; 95% CI: 1.3-2.3) and injection use (AHR=2.2; 95% CI=1.7-3.2). Individuals who were older than 14 years old and had initiated two or more substances within the same year had a significantly increased risk of an earlier transition to injection drug use (AHR=1.7; 95% CI: 1.2-2.4).

3.3 Predictors of HCV infection

The unadjusted and adjusted logistic models can be found in Table 6. After adjusting for age at time of interview, a one-year increase in transition time from first marijuana use (AOR= 0.91, 95% CI: 0.88-0.94) to injection decreased the odds of HCV infection by 9%. Similarly, a one-year increase in transition time from first pharmaceutical opioid use (AOR=0.91, 95% CI: 0.87-0.97) or polysubstance use (AOR=0.87, 95% CI: 0.81-0.94) to injection decreased the odds of HCV infection by 9% and 13%, respectively. The transition time from first alcohol intoxication to injection drug use was also a significant predictor of HCV infection and decreased the odds of HCV infection by 8% (AOR=0.92, 95% CI=0.88-0.96).

Table 1: Demographic characteristics and serostatus of nonurban PWID in Southwestern Connecticut (2008-2012)

Characteristics	No (%) or mean ± SD*	HCV positive*	HCV negative*	p-value†
Total (n)	462	181	266	
Age (mean)	35.3 ± 10.9	39.3 ± 10.8	32.3 ± 9.9	<0.001
Gender				
Male	288 (62.3)	109 (38.7)	173 (61.3)	0.30
Female	174 (37.7)	72 (43.6)	93 (56.4)	
Race				
White	386 (83.6)	157 (41.8)	219 (58.2)	0.21
Black	76 (16.5)	24 (33.8)	47 (66.2)	
Education				
Less than high school	87 (18.8)	38 (44.7)	47 (55.3)	0.68
High school graduate	195 (42.2)	75(39.5)	115 (60.5)	
More than high school	180 (39.0)	68 (39.5)	104 (60.5)	
Employed				0.08
No	328 (71.1)	136 (43.2)	179 (56.8)	
Yes	133 (28.9)	45 (34.4)	86 (65.6)	
Health insurance				0.04
None	97 (23.4)	29 (30.9)	65 (69.1)	
Government	277 (66.9)	120 (45.3)	145 (54.7)	
Private	40 (9.7)	14 (35.0)	26 (65.0)	
Monthly income				0.36
<$500	148 (32.0)	52 (35.9)	93 (64.1)	
$500-$999	99 (21.4)	43 (45.7)	51 (54.3)	
$1000-$1999	133 (28.8)	56 (43.7)	72 (56.3)	
≥$2000	82 (17.8)	30 (37.5)	50 (62.5)	
Resident town income				0.57
Above median state income	241 (52.2)	91 (39.2)	141 (60.8)	
At/below median state income	221 (47.8)	90 (41.9)	125 (58.1)	
Ever arrested				0.01
No	46 (10.3)	10 (21.7)	36 (78.3)	
Yes	401 (89.7)	171 (42.6)	230 (57.4)	
Ever jailed				0.002
No	81 (18.1)	22 (27.2)	59 (72.8)	
Yes	320 (71.6)	149 (46.6)	171 (53.4)	
Hepatitis B				<0.001
Positive	109 (24.4)	63 (57.8)	46 (42.2)	
Negative	337 (75.6)	117 (34.7)	220 (65.3)	
HIV				0.45
Positive	7 (1.6)	4 (57.1)	3 (42.9)	
Negative	440 (98.4)	177 (40.2)	263 (59.8)	

*Percentages may not sum to 100% due to rounding and numbers may not sum to totals due to missing data

† P-value for analysis of variance t-test (continuous variable) or χ^2 test or Fisher's test (categorical variable)

Table 2: Summary of the drug type used for first injection (N=458)

Drug type	N (%)*
Heroin	234 (51.1)
Other opioids	12 (2.6)
Cocaine	58 (12.7)
Other stimulants	7 (1.5)
Sedatives	5 (1.1)
2-3 drugs	130 (28.4)
4+ drugs	12 (2.6)

* Percentages may not sum to 100% due to rounding and number may not sum to totals due to missing data

Table 3: Mean age of initiating heroin use and injection drug use.

	N	Heroin Use mean ± SD	p-value*	N	Injection mean ± SD	p-value*
First alcohol intoxication			0.04			0.08
≤14 years old	206	22.6 ± 7.9		212	23.6 ±8.2	
>14 years old	152	24.3 ± 7.0		148	25.1 ±6.8	
First marijuana use			0.02			0.02
≤13 years old	201	22.7 ±7.7		216	23.5 ±7.7	
>13 years old	194	24.5 ±7.9		197	25.4 ±8.2	
First pharmaceutical opioid use			<0.001			<0.001
≤18 years old	142	21.0 ±6.0		147	22.0 ±6.1	
>18 years old	108	29.3 ±7.4		107	29.8 ±7.4	
Polysubstance use			0.60			0.95
≤14 years old	89	22.8 ±7.7		92	24.1 ±8.2	
>14 years old	54	23.5 ±7.4		53	24.1 ±7.0	

*P-value for Student's independent t-test.

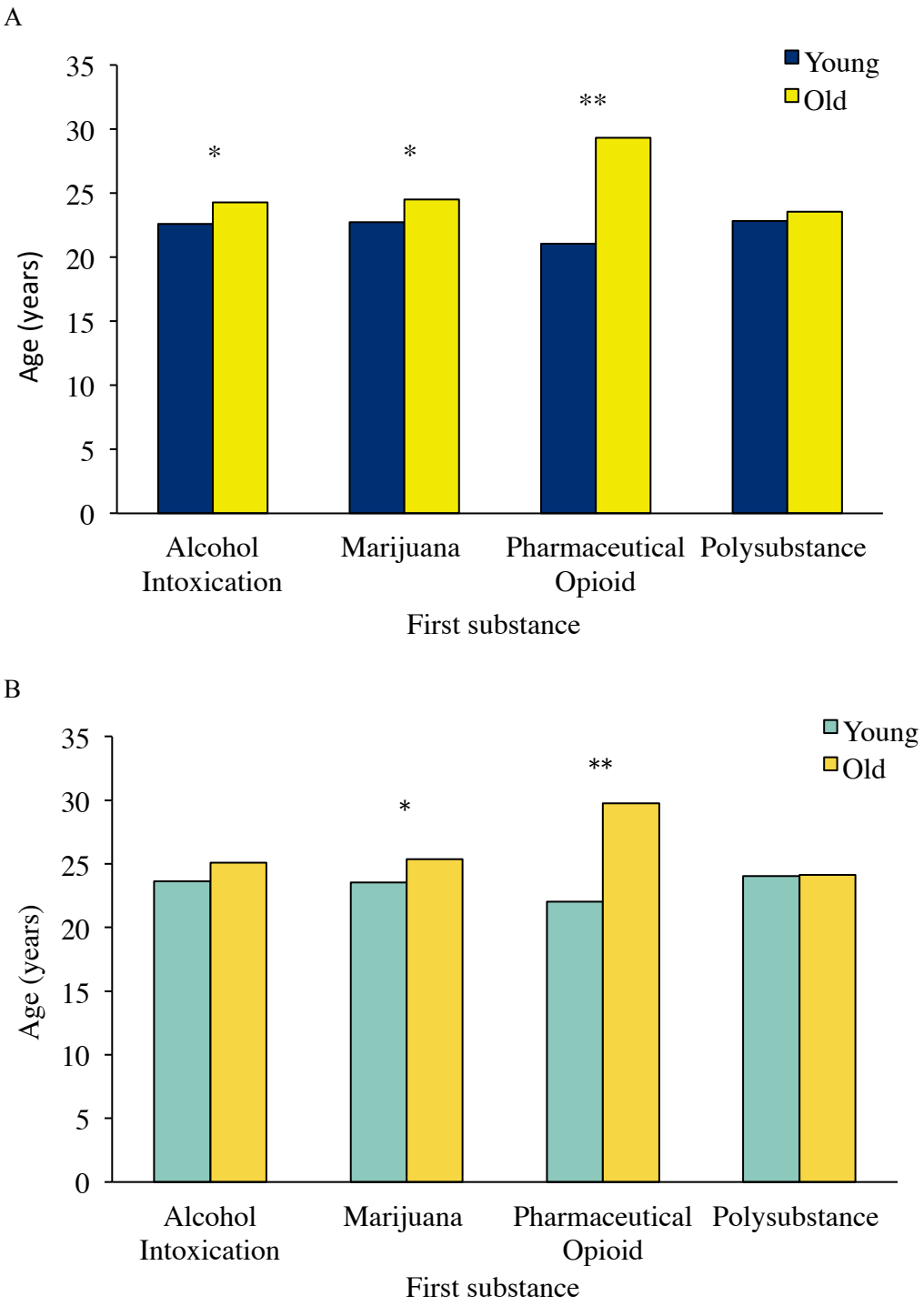


Figure 1: The mean age of transition to A) heroin or B) injection after initiation of first substance.

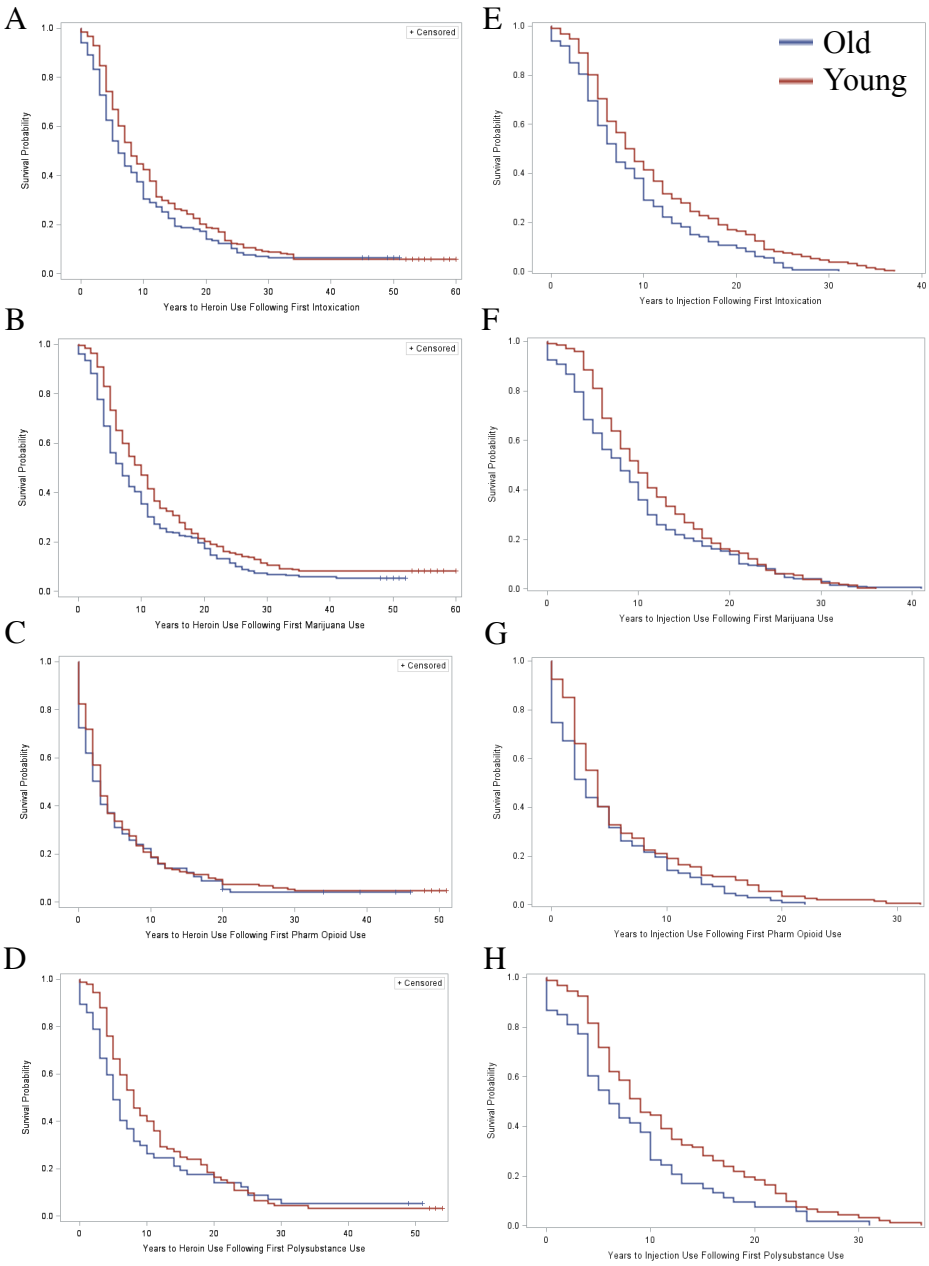


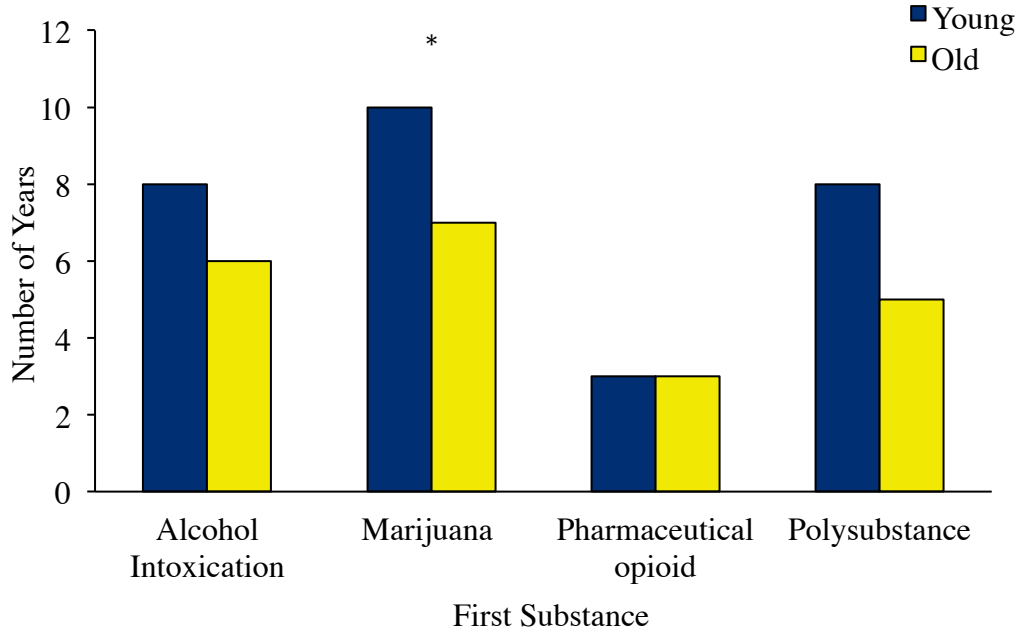
Figure 2: Kaplan-Meier curve showing the transition time from A) first alcohol intoxication, B) first marijuana use, C) first pharmaceutical opioid use, D) polysubstance use to first heroin use and from E) first alcohol intoxication, F) first marijuana use, G) first pharmaceutical opioid use, and H) polysubstance use to first injection, grouped by age of initiation.

Table 4: Median time between first substance use and transition to heroin use and to injection drug use.

	N	Heroin Transition time (95% CI)	p-value*	N	Injection transition time (95% CI)	p-value*
First alcohol intoxication			0.09			0.002
≤14 years old	204	8 (7-10)		212	8 (7-10)	
>14 years old	145	6 (5-8)		148	7 (6-8)	
First marijuana use			0.01			0.05
≤13 years old	201	10 (8-11)		216	10 (8-11)	
>13 years old	192	7 (5-8)		197	8 (6-9)	
First pharmaceutical opioid use			0.52			0.04
≤18 years old	142	3 (2-4)		147	4 (3-4)	
>18 years old	108	3 (2-3)		107	3 (2-4)	
Polysubstance use			0.25			0.02
≤14 years old	89	8 (6-11)		92	9 (7-11)	
>14 years old	54	5 (4-7)		53	6 (4-10)	

*P-value for Student's independent t-test.

A



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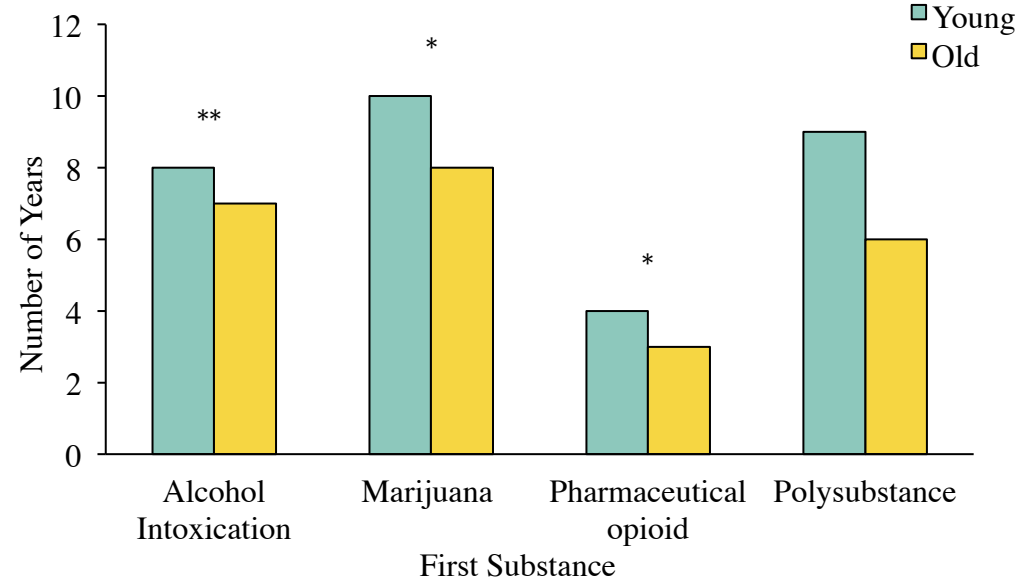

Figure 3: The median duration (years) between first substance initiation to transition of A) heroin or B) injection.

Table 5: Hazard ratios for the transition to heroin use and to injection drug use

	Transition to Heroin Use		Transition to Injection Use	
Covariate	Crude HR (95% CI)	Adjusted HR* (95% CI)	Crude HR (95% CI)	Adjusted HR* (95% CI)
First alcohol intoxication				
≤14 years old	1.0	1.0	1.0	1.0
>14 years old	1.2 (1.0-1.5)	1.7 (1.2-2.4)	1.4 (1.1-1.7)	1.6 (1.3-2.0)
First marijuana use				
≤13 years old	1.0	1.0	1.0	1.0
>13 years old	1.3 (1.1-1.6)	1.5 (1.2-1.8)	1.2 (1.0-1.5)	1.9 (1.3-2.6)
First pharmaceutical opioid use				
≤18 years old	1.0	1.0	1.0	1.0
>18 years old	1.1 (0.8-1.4)	1.7 (1.3-2.3)	1.3 (1.0-1.6)	2.3 (1.7-3.2)
Polysubstance use				
≤14 years old	1.0	1.0	1.0	1.0
>14 years old	1.2 (0.9-1.7)	1.2 (0.9-1.7)	1.5 (1.0-2.1)	1.7(1.2-2.4)

*Adjusted for age, gender, race, and education

Table 6: Summary of unadjusted and adjusted odds ratio for logistic regression analyses using transition time from usage of first substance to injection drug use as a predictor of HCV status.

Substance	Unadjusted OR	Adjusted OR*
Intoxication	0.99 (0.96-1.02)	0.92 (0.88-0.96)
Marijuana	0.98 (0.95-1.00)	0.91 (0.88-0.94)
Pharmaceutical Opioid	0.96 (0.92-1.01)	0.91 (0.87-0.97)
Polysubstance	0.98 (0.94-1.02)	0.87 (0.81-0.94)

*Adjusted for age at time of interview

4. Discussion

The purpose of this study was to examine the potential relationship between age of initiating a substance (first alcohol intoxication, first marijuana use, first pharmaceutical opioid, or polysubstance use) and the transition time to heroin use and to injection drug use. Overall, those who began using any of these substances at a younger age also began using heroin and/or injecting at a younger age compared to older initiates. The median ages of first alcohol intoxication and marijuana use in our study sample appeared to be slightly younger than the national averages for alcohol intoxication (16.2 years old), marijuana (16.2 years old) among recent initiates aged 12 and older [33]. Young marijuana and intoxication initiators ($\leq$ 13 years old and $\leq$ 14 years old, respectively) had slower transitions to heroin use and injection drug use than their older initiate counterparts. Older alcohol intoxication and marijuana initiates had shorter transition times and were at a significantly greater risk for early transition to heroin use and to injection drug use, after adjusting for age, gender, race and education. Young and old initiates of pharmaceutical opioids had no difference in the transition time to heroin, but those who began using later were at greater risk for quicker transition.

Among the possible factors contributing to differences in transition rate, factors worthy of further exploration include: easier access due to transportation availability, less parental supervision, and an established drug-use network, because they may contribute to an older individual's increased risk for early transition to heroin or injection drug use. According to the 2013 Monitoring the Future survey data, substances such as marijuana were less accessible to younger adolescents compared to 12th graders [34], suggesting that there were factors that allowed older adolescents to gain access to marijuana more easily. Those who began using multiple substances (alcohol intoxication, marijuana use, and pharmaceutical opioid) at a later age (>14 years old) did not have a significantly different risk of early transition to heroin compared to young initiates. However, they did have a significantly greater risk of early transition to injection drug use, when adjusted for age, race, gender and education. In fact, old and young initiators of polysubstance use did not begin heroin use or injection use at significantly different ages, suggesting that earlier initiation of polysubstances had little effect on drug trajectories.

It is known that HCV infection typically occurs within the first two years of injection initiation [15], thus it is of utmost importance to delay transition, as a form of HCV prevention. Our study supports the notion of the importance of postponing the transition to injection, because the odds of HCV infection decreases as the transition time increases. The decreased likelihood of transition may be because of character differences, such as level of risk aversiveness in the individuals who began injecting soon after initiation of a substance compared to those who did not. Most studies that have studied the transition from

first substance use to illicit drug use have focused on urban populations [20]. One other known study conducted among the rural Appalachian drug user population examined factors associated with transition rates from first illicit drug use to injection and found OxyContin use was associated with a faster transition [20]. However, in another study conducted in Maine, Grau *et al.* (2007) did not find a quicker progression to injection related to OxyContin use, but rather from polysubstance use, although in this study polysubstance use was restricted to initiation of multiple opioids in the same year [13]. Thus, more research is needed in nonurban populations to understand the importance of the type of initiation drug used for transition and the character differences that may influence transition behavior.

Although our current study offers important insights into drug transition and HCV risk, there are certain limitations that must be considered. The population should be considered one of convenience, because the respondent-driven sampling method yielded an insufficient number of productive seeds. At the time of the study design, information was not yet available on handling recruitment failure in RDS [4, 35]. As with any study that relies on participant recall and face-to-face interview methods, recall and social desirability bias regarding age of substance initiation may be present, but we do not know to what extent. The usage of computer-assisted interviewing may have helped to reduce social desirability bias [4]. In addition, transition times were calculated based on ages of initiation, not specific dates. We were unable to establish temporality for some individuals who began using a substance at the same age as initiating heroin use or injection. Lastly, other sociodemographic characteristics (i.e. homelessness, sexual and domestic abuse, mental illness, sexual behavior, and proximity to treatment centers), which could be associated with transition time and HCV infection, were not looked at in this study and need to be further investigated.

5. Conclusion

Little is currently known about the factors that may affect transition in nonurban populations of PWID, though our preliminary study demonstrates differences in early transition risk based on age of substance initiation. In addition, our study found that delaying transition could decrease the odds of HCV acquisition. Future studies should focus on understanding the mechanisms behind the differences in early transition risk, particularly for the development of targeted HCV prevention strategies, such as peer-based and educational interventions.

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