The association between non-injection drug use and hepatitis C infection among HIV-negative men who have sex with men

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Research Article

Keywords: Hepatitis C virus, non-injection drug use, men who have sex with men, latent class analysis, multinomial logistic regression, HIV negative MSM

Posted Date: October 4th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-946966/v1>

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Abstract

Background: This study investigated the association between drug use and Hepatitis C Virus (HCV) infection in HIV-negative men who have sex with men (MSM) who reported drug use but not injection drug use.

Methods: This cross-sectional study analyzed the data of 118 HIV-negative MSM who reported drug use but not injection drug use recruited from two inner-city communities between 2004 and 2007. Latent class analysis (LCA) was used to identify drug use latent classes. Multinomial logistic regression analysis was used to evaluate the association between drug use latent class and HCV infection.

Results: Four distinct latent classes of drug use were identified: (1) persons ≥ 42 years old who used only crack cocaine, (2) persons about 42 years old who used >2 drugs, (3) persons <42 years old who used >5 drugs, and (4) persons ≥ 42 years old who used >6 drugs. Class 4, persons ≥ 42 years old who used >6 drugs were significantly associated with HCV infection. Compared with persons about 42 years old who used >2 drugs, persons ≥ 42 years old who used >6 drugs had more than 16 times the odds of having HCV infection (adjusted OR = 16.9, 95%CI: 1.4-205.4), and compared with persons <42 years old who used >5 drugs, persons ≥ 42 years old who used >6 drugs were about 22 times as likely to have HCV infection (adjusted OR=21.8, 95%CI: 1.5-322.8).

Conclusions: The subgroup of MSM ≥ 42 years old with non-injection but multiple use of heroin, speedball, and methamphetamine, in addition to crack cocaine and marijuana, had high probability of HCV infection. Public health and education programs, as well as drug treatment and rehabilitation programs, should be developed for this high-risk subgroup to prevent HCV acquisition and transmission.

Background

Compared with the general population, men who have sex with men (MSM) are disproportionately affected by infectious diseases, such as HIV, syphilis and other sexually transmitted infections (STI) (CDC, 2017). MSM may also be disproportionately affected by HCV. HCV infection, which is a leading cause of liver failure and transplantation in the United States (Razavi et al., 2013), has been relatively understudied in MSM until 2000, when reports of an HCV epidemic or outbreaks in MSM began to emerge (Bottieau, Apers, Van Esbroeck, Vandenbruaene, & Florence, 2010; Giraudon et al., 2008; Urbanus, van de Laar, et al., 2009; Urbanus, van Houdt, van de Laar, & Coutinho, 2009; van de Laar et al., 2007; Wandeler et al., 2012). Most of these studies focused on MSM who are HIV positive, MSM who inject drugs, or both. Studies targeting HIV-negative and non-injection drug using MSM are needed.

Although HCV prevalence rates are comparable in HIV-negative MSM and in the general U.S. population (Blaxhult, Samuelson, Ask, & Hökeberg, 2014; Price et al., 2013), people who use drugs but do not inject drugs have been found to have a higher HCV infection rate (2.3–35.3%) than in the general population (1%) (Scheinmann et al., 2007). Furthermore, MSM have been reported with a higher rate of drug use than in heterosexual men (past month prevalence 16.3% vs 9.9%) (Cochran, Ackerman, Mays, & Ross, 2004).

These results showed a higher HCV infection rate in HIV-negative MSM with non-injection drug use than in the general population.

People who use drugs are usually heterogeneous with regard to drug types, because drug types are various and one individual may choose multiple drug types at the same time or different times. Analyzing types of drug use independently may overlook the complexity of multiple drug use or result in lack of generalizability. To analyze the drug use variables simultaneously, we applied latent class analysis to identify subgroups of drug use (Carlson, Wang, Falck, & Siegal, 2005; Kuramoto, Bohnert, & Latkin, 2011; Monga et al., 2007; Sherman et al., 2009; Wittchen et al., 2009), and further explored the association between drug use subgroups and disease. In one US internet-based MSM sample, a distinct multiple drug use group was identified (McCarty-Caplan, Jantz, & Swartz, 2014). Another study recruited a similar sample of MSM and found that high multiple drug using MSM were more likely to report unprotected anal intercourse, and STIs (Yu, Wall, Chiasson, & Hirshfield, 2015). In a Malaysia Asia internet-based MSM sample, an amphetamine-type stimulant class was associated with sexual risk behavior and the infection of HIV and STIs, compared to a low-risk drug use group (Lim et al., 2015).

To the best of our knowledge, there are no studies of HCV infection targeting HIV-negative MSM with non-injection drug use. To fill this knowledge gap, this study applied LCA to identify latent classes among MSM who reported drug use not no injection drug use, and examined the association between latent classes and HCV infection in HIV-negative MSM. It was hypothesized that, first, there are distinct latent classes in the target population, and, second, one or more latent classes are associated with HCV infection. The results of this study may provide insight for HCV prevention and health education programs targeted at HIV-negative MSM with non-injection drug use.

Methods

Samples from DASH project

Data for the present study were collected from a cohort of drug users enrolled in the Drugs, AIDS, STDs, and Hepatitis (DASH) project, a community-based intervention study among a non-treatment drug-using population for HIV, HBV, and HCV prevention (Hwang et al., 2010). The DASH project recruited individuals from two highly endemic drug-using urban neighborhoods in Houston, TX, from February 2004 to October 2007. Participants were recruited by outreach workers using a chain referral approach. People were eligible for the study if they were: 18 years old or above, had local residence, self-reported use of illegal and non-medical prescribed drugs including cocaine or heroin in the last 48 hours and confirmed presence of drug metabolites by urinalysis (OnTrak Varian Testik, Palo Alto, CA.), and willingness to sign the informed consent form for HIV, HBV, and HCV testing.

Individuals with negative HIV and HBV screening tests were enrolled into the baseline study. Enrollment interviews were conducted using verbally administered questionnaires via computer-assisted personal interview method (CAPI, QDS, Bethesda, MD). Baseline data were from the enrollment interview. All data

collection procedures and laboratory protocols were approved by the Committee for the Protection of Human Subjects at the University of Texas Health Science Center at Houston.

Data for this study were restricted to 118 participants who reported male-to-male sex and did not report any injection drug use.

Measures

For sociodemographic characteristics, information was collected on age, race/ethnicity, sexual orientation, education level, marital status, working status, income level, living arrangement, jail history of more than 24 hours, and drug treatment history. Sexual behavior variables included number of male sexual partners in the past 30 days, frequency of condom use, trading sex for money or drugs in the past 30 days, and trading money or drugs for sex in the past 30 days. Disease status comprised self-reported STI history for gonorrhea, herpes, chlamydia, and trichomoniasis, as well as HCV infection status, screened by HIV1/2 antibodies, HBsAg and HCV antibody Combo test (Core Diagnostics, United Kingdom), confirmed by Microparticle enzyme immunoassay test (Abbott Laboratories, Chicago, IL). HCV infection was defined as HCV antibody positive. Also, history of blood transfusion, and occupational exposure to blood was collected during the enrollment interview.

Drug use variables and age were used as latent class indicators. Drug use variables included the participants' response to the question, "Have you ever used the following drugs: crack cocaine, methamphetamine, marijuana, alcohol, fry^[1], powder cocaine, heroin, speedball (a mixture of heroin and cocaine) and codeine syrup?" Drug use indicators were denoted as: "never use" (0) or "have ever used" (1). Also, age was considered an indicator variable because age has been associated with drug use types. (Bluthenthal, Wenger, Chu, Bourgois, & Kral, 2017; Golub, Johnson, & Dunlap, 2005) Based on a median age of 42, participants were categorized as "< 42 years old" (0) or "≥ 42 years old".

Statistical analysis

We applied LCA to identify drug use latent classes among our MSM sample. An LCA model uses a maximum likelihood approach to identify subgroups or classes of individuals with similar patterns of responses to a set of indicator variables (A. L. McCutcheon, 1987; Whitesell et al., 2006). Based on indicator variables, LCA assigns each individual a probability of membership in the postulated multilevel latent variable (Allan L McCutcheon, 2002). LCA assumes homogeneity within a class, heterogeneity among classes, and that the difference in response to items within a class is only due to random error (A. L. McCutcheon, 1987; Whitesell et al., 2006).

We started with a 1-class model and increased the number of classes through 6-class models. To obtain the global not local maxima for each model, we used 5,000 random starts. We used BIC (the Bayesian Information Criteria), BLRT (the parametric bootstrap likelihood ratio test), and LMR (the Lo-Mendell-Rubin adjusted likelihood ratio test) to select the model. In addition, we used entropy, a standardized

summary measure of the classification accuracy, to evaluate the precision of individual assignment based on their model-based posterior probabilities. Entropy ranges from 0 to 1, and the higher entropy value reflects the better classification (Ramaswamy, DeSarbo, Reibstein, & Robinson, 1993). We based our final latent class solution on not only statistical significance, but also substantive criteria, e.g., the epidemiological explanation of drug use.

After latent class identification, we conducted logistic regression models to examine the association between class membership and HCV status, sociodemographic characteristics, sexual behaviors, and sexual transmitted disease history. We used the AUXILIARY (r) option (Muthn & Muthn, 2012) for the multinomial logistic regression estimation. This technique incorporates the posterior-probabilities of membership into the estimation procedure, and helps examine the fidelity and utility of the specific latent class profiles (Petrs & Masyn, 2010). We conducted bivariate associations of latent class of drug use with each independent variable. Independent variables with a P-value less than 0.25 were entered into the joint model, which allowed us to evaluate the adjusted relationships between membership in a particular drug use class and HCV infection. We used Mplus 6.1 (Muthn & Muthn, CA) to conduct the LCA model building and multi-nominal and multivariable logistic regression and SAS 9.4 (Cary, NC) to manage the data.

[1] Fry: embalming fluid and phencyclidine (PCP)-laced cigarettes or marijuana sticks

Results

In the DASH parental project study, the prevalence of HCV was 36.1% among 2,800 drug users who were contacted for HIV/HBV/HCV screening. The predominant risk characteristic associated with HCV infection was injection drug use (70% prevalence). (Hwang & Grimes, 2012). Among 273 MSM who reported drug use not including injection drug use, the HCV prevalence was 14.7%. Only age was significantly associated with HCV infection. Compared to participants who were less than 42 years old, those age 42 or older had 2.1 times the odds of having HCV infection (95%CI: 1.4-3.0).

Among 273 MSM who reported drug use not including injection drug use, we analyzed 118 MSM who participated in the baseline interview, among whom 21 (17.8%) were infected with HCV. Table 1 presents the sociodemographic characteristics and behavioral variables for the analytical sample. For sociodemographic characteristics, the age of the participants ranged from 19 to 61 years old with the mean of 39.6 years old (IQR: 35-46), 83% were African American, 83% reported sexual orientation as bisexual or homosexual, 76% had less than a high school education or completed high school only, 65% were single, 50% worked less than 14 days in the past month, 50% had an income less than 400 dollars in the past month, 46% had been homeless at least once, 76% had been arrested and spent more than 24 hours in jail, and 35% never received drug treatment. For sexual risk behaviors, 41% of the participants had 0 or 1 male sexual partners in the past month, about two thirds of them used condoms less than half of the time while having sex, about two thirds of the participants had traded sex for money or drugs in the past month, more than half had traded money for drugs or sex in the past month. Regarding disease

history, 45% had been diagnosed with STIs. Regarding drug use behavior, the majority of participants had used multiple drugs (defined as had ever used more than 2 drugs), and the most prevalent drug types were crack cocaine (98%), marijuana (89%), and alcohol (86%). The prevalence of other types of drug use were 57% for powder cocaine, 22% for codeine, 21% for fry, 14% for methamphetamine, 6.8% for heroin, and 3.4% for speedball.

Table 1
 Characteristics of 118 HIV-negative MSM who reported drug use but did not report
 injection drug use in Houston, TX

Characteristics	n	%
Latent class indicators ^a		
Crack cocaine	116	98.3
Methamphetamine	17	14.4
Marijuana	105	89.0
Alcohol	101	85.6
Fry	25	21.2
Powder cocaine	67	56.8
Heroin	8	6.8
Speedball	4	3.4
Codeine	26	22.0
42 years old or above	59	50
Sociodemographic characteristics		
African American	98	83.1
Self-reported homosexual or bisexual	98	83.1
Education level (less than or equal to high school)	90	76.3
Marital status (single)	77	65.3
Worked less than 14 days in past 30 days	58	49.2
Income less than 400 dollars in the past month	70	59.3
Homeless	54	45.8
Had been in jail for more than 24 hours	90	76.3
Never received drug treatment	41	34.7
Sexual behaviors		
Had 0 or 1 male sexual partner in the past month	48	40.7
Condom use frequency (<=50%)	71	60.7
Traded sex for money or drugs in the past month	74	62.7

^a These variables refer to the response to the question: "have you ever used this drug"

Characteristics	n	%
Traded money or drugs for sex in the past month	68	57.6
Diseases status		
Had sexual transmitted disease history	53	44.9
Blood exposure		
Had blood transfusion history	4	3.4
Had occupational blood exposure history	7	5.9
a These variables refer to the response to the question: “have you ever used this drug”		

For LCA, Table 2 presents the results of statistics and entropy for 1- through 6- latent classes. Although the BIC value was the lowest at the 2-class model solution, LMR supported for all 2- through 5- class model (p-value <0.05) and BLRT supported for 2- through 4- class model. Entropy showed that all 3- through 6- class models had satisfied precision (entropy >0.8). Therefore, both 3- and 4- class models were preferable. Based on statistical significance and practical utility, we selected the 4-class model as the best fit model.

Table 2
Statistics and entropy of latent class analyses

classes	LL ^a	Free parameters	BIC ^b	LMR ^c	BLRT ^d	Entropy
1	-462.630	10	972.966	NA	NA	NA
2	-430.427	21	961.039	0.0001	0.0000	0.731
3	-418.644	32	989.950	0.0177	0.0100	0.957
4	-406.801	43	1018.742	0.0424	0.0400	0.963
5	-400.104	54	1057.826	0.0115	0.4000	0.957
6	-394.546	65	1099.186	0.1469	0.6200	0.978

Figure 1 shows the estimated probability of the 4-class model. Participants in class 1, accounted for 6.5% of the sample, had high probability (>95%) of using only crack cocaine and the lowest probability of using all other types of drugs, with 75% probability of being 42 years old or above. We referred to class 1 as “*persons >=42 years old who used only cocaine*”. Class 2 members accounted for 70.3% of the sample, had high probability (>90%) of using crack cocaine, marijuana, and had moderate probability

(50%) of using powder cocaine, with a half of the probability of being 42 years old or above. We referred to class 2 as *“persons about 42 years old who used >2 drugs”*. Class 3 members accounted for 20.1% of the participants, had high probability (>90%) of using crack cocaine, marijuana, powder cocaine, and especially compared with all other classes, class 3 members had the highest probability of using fry and codeine; the probability of being 42 years old or above was only 35%. We referred to class 3 as *“persons <42 years old who used >5 drugs”*. Individuals in class 4 accounted for 3.2% of the sample, had high probability of using all types of drugs except for fry and codeine, specifically, the probability of using methamphetamine, heroin, and speedball were the highest among individuals in class 4 compared to all other classes, and the probability of being 42 years old or above were very high (>99%). We referred to class 4 as *“persons >=42 years old who used>6 drugs”*.

Table 3 presents the results of our bivariate multinomial logistic regression. We found that only HCV status was significantly associated with drug use latent classes. Compared with the members in other classes, class 4 members had the highest possibility of having HCV infection. The odds of having HCV infection among class 4 members was 14 times (OR=14.2, 95%CI: 1.3-157.4) the odds of having HCV infection among those who in class 2, and was 20 times (crude OR=20.5, 95%CI: 1.4-291.7) the odds of having HCV infection among those who in class 3. The probability of having HCV also showed higher in class 4 members than class 1 members, but the results was not statistically significant (crude OR=7.8, 95%CI: 0.5-134.7). For the associations between drug use classes with other variables, such as sociodemographic characteristics, sexual behaviors, self-reported STI history, blood transfusion history, and occupational blood exposure history, all the results were not statistically significant.

Table 3

Bivariate associations between latent class membership and characteristics of 118 HIV-negative MSM who reported drug use but not injection drug use in Houston, TX

Characteristics	Class 4 vs 1	Class 4 vs 2	Class 4 vs 3	Class 1 vs 2	Class 1 vs 3	Class 3 vs 2
	cOR (95%CI)*	cOR (95%CI)	cOR (95%CI)	cOR (95%CI)	cOR (95%CI)	cOR (95%CI)
Sociodemographic						
African American vs Caucasian or Hispanic	14621447 (0.0-I)	1.5 (0.1-16.3)	2.7 (0.2-40.2)	0.0 (0.0-I)	0.0 (0.0-I)	0.5 (0.1-2.4)
Homosexual or bisexual vs heterosexual	0.0 (0.0-I)	0.0 (0.0-I)	0.0 (0.0-I)	2.2 (0.4-12.7)	0.9 (0.1-6.3)	2.3 (0.7-7.2)
Less than or equal to high school vs higher than high school	0.0 (0.0-I)	0.4 (0.0-3.7)	0.3 (0.0-3.1)	9175065 (0.0-I)	6382051 (0.0-I)	1.4 (0.4-4.7)
Single vs married, live with partner, separated, divorced, widowed	20.5 (0.0- 2.12E189)	5.5 (0.5-58.6)	4.0 (0.3-47.6)	0.3 (0.0- 2.75E187)	0.2 (0.0- 2.03E187)	1.4 (0.5-3.6)
Days of working in the past month: <14 days vs >=14 days	1980777 (0.0-I)	17175594 (0.0-I)	27371147 (0.0-I)	8.7 (0.0- 1.99E192)	13.8 (0.0- 3.17E192)	0.6 (0.2-1.7)
Income in the past month: <400 dollars vs >= 400 dollars	11.6 (0.0-I)	64.8 (0.0-I)	85.0 (0.0-I)	5.6 (0.0- 2.27E198)	7.3 (0.0- 2.98E198)	0.8 (0.3-2.0)
Ever homeless vs never homeless	0.2 (0.0-3.4)	0.4 (0.0-4.4)	0.5 (0.0-6.2)	2.0 (0.4-9.7)	2.5 (0.4-14.3)	0.8 (0.3-2.1)
Had been in jail for more than 24 hours: Yes vs No	7195742 (0.0-I)	4239687 (0.0-I)	2340792 (0.0-I)	0.6 (0.1-3.0)	0.3 (0.0-2.2)	1.8 (0.5-6.3)

Characteristics	Class 4 vs 1	Class 4 vs 2	Class 4 vs 3	Class 1 vs 2	Class 1 vs 3	Class 3 vs 2
	cOR (95%CI)*	cOR (95%CI)	cOR (95%CI)	cOR (95%CI)	cOR (95%CI)	cOR (95%CI)
Never received drug treatment vs received drug treatment	0.7 (0.0-12.0)	0.6 (0.1-6.2)	1.2 (0.1-15.6)	0.8 (0.1-4.6)	1.8 (0.3-12.1)	0.5 (0.2-1.5)
Sexual behavior						
No. of male sexual partners in the past month: 0 or 1 vs >1	0.0 (0.0-I)	0.0 (0.0-I)	0.0 (0.0-I)	1.2 (0.2-6.1)	1.0 (0.2-5.6)	1.2 (0.5-3.3)
Condom use frequency while having sex: <=50% vs >50%	0.7 (0.1-10.0)	0.8 (0.1-7.2)	0.6 (0.1-5.8)	1.1 (0.2-5.2)	0.8 (0.1-4.5)	1.4 (0.5-3.9)
Traded sex for money or drugs in the past month Yes vs No	2.8 (0.2-42.8)	1.7 (0.2-17.8)	1.3 (0.1-16.0)	0.6 (0.1-2.9)	0.5 (0.1-2.7)	1.2 (0.5-3.4)
Traded money or drugs for sex in the past month Yes vs No	2.5 (0.2-39.1)	2.3 (0.2-24.6)	1.2 (0.1-14.9)	0.9 (0.2-4.5)	0.5 (0.1-2.9)	1.9 (0.7-5.2)
Blood exposure history						
Had blood transfusion Yes vs No	12310954 (0.0-I)	14.7 (1.0- 220.7)	9.7 (0.0- 3.07E257)	0.0 (0.0-I)	0.0 (0.0-I)	1.5 (0.0- 4.83E256)
Had occupational blood exposure Yes vs No	2.0 (0.0-I)	0.0 (0.0-I)	6.3 (0.0-I)	0.0 (0.0-I)	3.1 (0.0-I)	0.0 (0.0-I)
Disease history						
Had STI*** Yes vs No	1.6 (0.1-25.4)	4.4 (0.4-46.4)	2.1 (0.2-25.0)	2.8 (0.5-14.0)	1.4 (0.2-7.9)	2.1 (0.8-5.4)

Characteristics	Class 4 vs 1	Class 4 vs 2	Class 4 vs 3	Class 1 vs 2	Class 1 vs 3	Class 3 vs 2
	cOR (95%CI)*	cOR (95%CI)	cOR (95%CI)	cOR (95%CI)	cOR (95%CI)	cOR (95%CI)
Had HCV infection	7.8	14.2 **	20.5 **	1.8	2.6	0.7
Yes vs No	(0.5- 134.7)	(1.3- 157.4)	(1.4- 291.7)	(0.3-10.6)	(0.3-21.8)	(0.2-3.0)
* cOR: crude odds ratio ** P<0.05 *** STI: Sexually transmitted infections						

Table 4 presents the results of our multivariable regression model. We entered drug treatment history, self-reported STI history and trading money or drugs for sex in the past month in the model (these variables had p-values<0.25 in the bivariate analysis) to adjust for the association between drug use class and HCV infection. The results showed that HCV infection status was significantly associated with drug use classes. Compared with class 2 members, class 4 members had close to 17 times the odds of having HCV infection (adjusted OR = 16.9, 95%CI: 1.4-205.4), and compared with class 3 members, class 4 members had close to 22 times the odds of having HCV infection (adjusted OR=21.8, 95%CI: 1.5-322.8), controlling for drug treatment history, self-reported STI history and trading money or drugs for sex in the past month.

Table 4

Multivariable association between latent class membership with characteristics in 118 HIV-negative MSM who reported drug use but not injection drug use in Houston, TX

Characteristics	Class 4 vs 1	Class 4 vs 2	Class 4 vs 3	Class 1 vs 2	Class 1 vs 3	Class 3 vs 2
	aOR* (95%CI)	aOR (95%CI)	aOR (95%CI)	aOR (95%CI)	aOR (95%CI)	aOR (95%CI)
Never received drug treatment vs received drug treatment	0.8 (0.0- 17.0)	0.7 (0.1- 9.8)	1.2 (0.1- 19.7)	0.9 (0.1- 5.1)	1.5 (0.2- 11.0)	0.6 (0.2- 1.9)
Had STIs*** vs Never had STI	1.9 (0.1- 33.5)	5.3 (0.4- 65.3)	2.7 (0.2- 36.6)	2.8 (0.5- 14.6)	1.4 (0.2- 8.6)	2.0 (0.7- 5.3)
Traded money or drugs for sex in the past month vs never traded money or drugs for sex in the past month	2.5 (0.1- 48.4)	2.4 (0.2- 33.2)	1.4 (0.1- 21.6)	1.0 (0.2- 4.8)	0.6 (0.1- 3.4)	1.7 (0.6- 5.0)
Had HCV infection vs Did not have HCV infection	8.5 (0.5- 154.0)	16.9 ** (1.4- 205.4)	21.8 ** (1.5- 322.8)	2.0 (0.3- 12.2)	2.6 (0.3- 22.2)	0.8 (0.2- 3.5)
* aOR: adjusted odds ratio						
** P<0.05						
*** STI: Self-reported sexually transmitted infection						

Discussion

In this study, we applied LCA to identify latent classes among MSM who reported drug use but did not report injection use of drugs. We found four distinct latent classes, which were class 1, persons ≥ 42 years old who used only crack cocaine; class 2, persons about 42 years old who used >2 drugs; class 3, persons <42 years old who used >5 drugs; and class 4, persons ≥ 42 years old who used >6 drugs. We also found associations between certain latent classes of drug use and HCV infection. After adjusting for drug treatment history, self-reported STI history, and behavior of trading money or drugs for sex in the past month, we found that persons ≥ 42 years old who used >6 drugs had close to 17 times the odds of having HCV infection, compared with persons about 42 years old who used >2 drugs, and close to 22 times the odds of having HCV infection, compared with persons <42 years old who used >5 drugs.

Among participants who were 42 years old or above, the membership of drug use latent class was polarized. Members in one class (class 1) only used crack cocaine, whereas members in the other class

(class 4) used multiple drugs, including crack cocaine, marijuana, powder cocaine, methamphetamine, heroin, and speedball. The members in class 4 had a higher HCV infection probability than those who were in class 1, but the difference was not statistically significant. However, we need to interpret this non-significant result cautiously, because the sample sizes in the two classes accounted for only 3.2% and 6.5% of the sample, respectively, which limited the statistical power of the study to detect the differences in HCV infection probabilities between these two classes.

The mean age for the class 3 members was slightly lower than that for the class 2 members. The class 3 members had higher probability of using fry and codeine than the class 2 members, which is consistent with previous reports in the 1990s of fry (Modesto-Lowe & Petry, 2001; Peters Jr et al., 2005) and codeine abuse (Elwood, 2001; Peters Jr et al., 2007), especially among teenagers. The results of the present study showed that compared with participants who used crack cocaine and marijuana, those who additionally used fry and codeine did not have a higher probability of HCV infection. One reason may be that people normally take fry by smoking it and codeine in the form of syrup, pill, or drinks (mixed with soda). All these administrative routes have a lower likelihood of blood exposure that may lead to HCV infection and transmission. However, studies have reported an increase of sexual risk behavior in fry or codeine drug users (Peters Jr et al., 2007), but these studies were not restricted to MSM. The present study, which was restricted to MSM, found that the use of fry or codeine were not associated with sexual risk behaviors.

By comparing latent classes of drug use with different ages, we found an interaction effect between age and drug use types on the probability of HCV infection. This finding indicates that age and drug use types were both associated with HCV infection, and that differences in age were linked to different preference of drug use types. The participants who had multiple use of heroin, speedball, and methamphetamine, in addition to the commonly used crack cocaine and marijuana, were all 42 years old or above, which formed a latent class that had a much higher HCV infection probability than that of other latent classes. On the one hand, some previous studies revealed that individuals born between 1945-1965 had a higher HCV infection rate than that of other individuals; conversely, other previous studies implied that the use of heroin, speedball, and methamphetamine may relate to HCV infection from several perspectives. First, repeated intranasal use of heroin, cocaine (speedball is heroin mixed with cocaine), and methamphetamine may cause mucosal trauma and hyperemia (Bakhshaei, Khadivi, Sadr, & Esmatinia, 2013; Blaise, Vanhootehem, & De La Brassinne, 2007; Peyrière et al., 2013; Trimarchi et al., 2006), and HCV has been detected in nasal secretions (Aaron et al., 2008) in people with HCV infection. Second, drug use paraphernalia are often shared among people who use drugs, and HCV RNA may remain in the paraphernalia for up to 16 hours (Kamili, Krawczynski, McCaustland, Li, & Alter, 2007). Third, people who use heroin, speedball, and methamphetamine may be exposed to social networks with a higher HCV infection rate than those who use other drugs, because a proportion of people who use heroin, speedball, and methamphetamine inject these drugs, and 40%-90% of people who inject drugs are infected with HCV (Gerberding, 1994; Hagan, Pouget, Des Jarlais, & Lelutiu-Weinberger, 2008). However, some studies have not found that sharing straws or dollar bills when snorting drugs among people who do not report injection drug use is associated with HCV infection (Gyarmathy, Neaigus, Miller, Friedman, & Jarlais, 2002;

Howe et al., 2005). More research is needed to determine whether sharing equipment for non-injection drug use is a transmission route of HCV or not.

We cannot directly compare the present LCA findings with those of previous LCA findings because of different recruitment strategies, indicator variables, and the disease of interest. However, our findings are consistent with other findings demonstrating high rates of infectious diseases, such as HIV, among multiple drug users (Buchacz et al., 2000; Chitwood, Comerford, & Sanchez, 2003; Drumright & Colfax, 2009; Vallejo et al., 2008). LCA studies in MSM have demonstrated that multiple drug use is also associated with increased transmission of STIs by disinhibiting sexual risk behavior (Lim et al., 2015; Yu et al., 2015); the present study did not find an association between multiple drug use and STIs. One reason of this lack of association may be that individuals with HIV and/or HBV infection were excluded from the baseline data of DASH project, which may in turn, lead to the exclusion of individuals also coinfecting with STIs; thus, underestimating the effect of multiple drug use on STIs or risky sexual behavior in our sample of MSM.

This study had some limitations. First, we had small sample size for some drug use subgroups identified by LCA. During analysis, we tested multiple combinations of different variable classifications, and only the reported subgroup solution showed a significant association with HCV infection. However, although this solution was statistically significant, it also had very large confidence intervals; thus, we must interpret the results with caution. Second, for some variables assessing sexual risk behaviors, this study might not have sufficient power to identify their effects on HCV transmission. Third, the route of drug use, and information regarding sharing equipment for drug use were not collected in this study, which may provide crucial information on HCV transmission route in this population (Tortu, McMahon, Pouget, & Hamid, 2004). Fourth, although drug use was verified by lab testing, drug use types and sexual risk behaviors were self-reported, which may have led to underreporting. Fifth, the cross-sectional study design may not confirm the temporality of the risk behaviors and HCV infection. Lastly, some information potentially related to sexual transmission of HCV was not collected in this study, e.g., drugs related to sex (MDMA, LSD, etc.), and sexual behaviors such as anal sex and group sex. Future studies are warranted with larger sample size, collecting additional information on administrative routes of drug use, sex-related drugs, and detailed sexual risk behaviors of MSM. Further, a longitudinal study design may help clarify the temporality of risk behaviors and HCV infection and explore the transition between drug use subgroups, which may provide insightful understanding of association between drug use behavior and the risk of HCV infection.

Despite these limitations, this study has several strengths. To the best of our knowledge, this is the first study to evaluate the association of latent class of non-injection drug use and HCV infection among HIV-negative MSM by using latent class analysis. Because LCA reduced the dimension of drug use types, this study discovered and evaluated the interaction effect between age and multiple drug use types on HCV infection, which very few studies have reported. In addition, this study excluded individuals with HIV and/or HBV infection; thus, although it led to a smaller sample size for this study, we demonstrated that

in the absence of HIV and HBV, there was still a strong association between the interaction of age and multiple drug use types on HCV infection.

Conclusion

In conclusion, we found four distinct latent classes of drug use among MSM: (1) persons ≥ 42 years old who used only crack cocaine, (2) persons about 42 years old who used >2 drugs, (3) persons <42 years old who used >5 drugs, and (4) persons ≥ 42 years old who used >6 drugs. Persons ≥ 42 years old who used >6 drugs was associated with increased probability of HCV infection. Health education and promotion programs geared towards this subgroup of MSM are needed to increase the awareness of HCV infection, and subsequently increase testing and treatment rates for HCV. Furthermore, drug treatment programs or rehabilitation programs are also needed to reduce the physical damage of multiple drug use and the probability of acquiring or transmitting HCV, especially among heavy multiple drug use MSM.

Declarations

Ethics approval and consent to participate

We confirm that any aspect of the work covered in this manuscript that has involved human patients has been conducted with the ethical approval of all relevant

bodies and that such approvals are acknowledged within the manuscript.

Consent for publication

We confirm that the participant of the study provided written informed consent for the publication of any associated data.

Availability of data and material

We confirm that all datasets on which the conclusions of the paper depend are available to readers.

Competing interests

We confirm that there are no known conflicts of interest associated with this publication.

Funding

This study was funded by The National Institute of Drug Abuse (NIDA# 1R01DA017505). This work was funded (in part) by a Research Training Award for Cancer Prevention Post-Graduate Training Program in Integrative Epidemiology from the Cancer Prevention & Research Institute of Texas, grant number RP160097 (PI: M. Spitz).

Authors' contributions

JZ analyzed the data. JZ wrote the manuscript with support from CM and AN. CG and KF verified the analytical methods. LYH helped supervise the project. All authors read and approved the final manuscript.

Acknowledgements

We thank the participants who volunteered biological specimens and data, the DASH staff who collected the data, and Dr. Dimpy Shah who managed the data.

Abbreviations

HCV

Hepatitis C virus

MSM

Men who have sex with men

LCA

Latent class analysis

STI

Sexually transmitted infections

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Figures

Figure 1 Probability of each indicator variable in each class of 4-latent class model

Figure 1

The association between non-injection drug use and hepatitis C infection among HIV-negative men who have sex with men. Probability of each indicator variable in each class of 4-latent class model. Note: Class 1 (6.5%): persons ≥ 42 years old who used only crack cocaine; Class 2 (70.3%): persons about 42 years old who used >2 drugs; Class 3 (20.1%): persons <42 years old who used >5 drugs; Class 4 (3.2%): persons ≥ 42 years old who used >6 drugs.