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Progression to regular heroin use: Examination of patterns, predictors, and consequences

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Abstract

Background—The present study retrospectively evaluated the chronology and predictors of substance use progression in current heroin-using individuals.

Methods—Out-of-treatment heroin users (urinalysis-verified; $N = 562$) were screened for laboratory-based research studies using questionnaires and urinalysis. Comprehensive substance use histories were collected. Between- and within-substance use progression was analyzed using stepwise linear regression models.

Results—The strongest predictor of onset of regular heroin use was age at initial heroin use, accounting for 71.8% of variance. The strongest between-substance predictors of regular heroin use were ages at *regular* alcohol and tobacco use, accounting for 8.1% of variance. Earlier onset of regular heroin use (≤20 years) vs. older onset (≥30 years) was associated with a more rapid progression from *initial* to *regular* use, longer duration of heroin use, more lifetime use-related negative consequences, and greater likelihood of injecting heroin. The majority of participants (79.7%) reported substance use progression consistent with the gateway hypothesis. Gateway-inconsistent individuals were more likely to be African-American and to report younger age at initial use, longer duration of heroin use, and more frequent past-month heroin use.

Conclusions—Our findings demonstrate the predictive validity and clinical relevance of evaluating substance use chronology and the gateway hypothesis pattern of progression.

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Contributors

EAW was responsible for conceptualizing the data analysis, analyzing the data, creating figures and tables, and drafting the manuscript. JJKS contributed to authoring the manuscript and assembled the database. LHL contributed to psychiatric screening and edited the manuscript. MKG contributed to the study design and data coordination, and edited the manuscript. All authors have reviewed the manuscript content and approved the final version for publication.

Conflict of interest

All authors declare no conflict of interest with respect to the conduct or content of this work.

Keywords

Substance use progression; Gateway hypothesis; Opioid; Heroin use disorder

1. Introduction

1.1. Background

Global opioid use increased significantly in the past decade (SAMHSA, 2013; UNODC, 2013). Opioid use is implicated in more substance use-related overdose deaths than any other drug class (UNODC, 2013). Moreover, an estimated 14 million people worldwide administer drugs via injection (common among heroin users) which is associated with increased risk of contracting HIV and blood-borne diseases (Chitwood, Comerford, & Sanchez, 2003; UNODC, 2013). Heroin use is associated with severe health consequences and, for purposes of this study, will be conceptualized as an ‘end-point’ substance-use phenotype.

Previous research characterized substance-use progression and identified accurate predictors of future substance use disorders that can inform prevention and/or early intervention strategies (Hser, Longshore, & Anglin, 2007; Lee, Winters, & Wall, 2010; Vanyukov et al., 2012). One robust predictor of earlier future substance use disorders is earlier age at initial use of that substance (Chen, Storr, & Anthony, 2009; Windle & Windle, 2012). This intuitive finding has been repeatedly observed for use of alcohol (Brook, Brook, Zhang, Cohen, & Whiteman, 2002; DeWit, Adlaf, Offord, & Ogborne, 2000; Grant & Dawson, 1997; Grant, Stinson, & Harford, 2001; Nelson & Wittchen, 1998); nicotine (Breslau, Fenn, & Peterson, 1993; Hu, Griesler, Schaffran, Wall, & Kandel, 2012); and marijuana (Chen, O’Brien, & Anthony, 2005; Ellickson, Martino, & Collins, 2004). While informative, these findings are limited to within-substance progression. The majority of substance using individuals reported initial poly-substance experimentation that progressed to problematic use and dependence (Moss, Chen, & Yi, 2013; Olthuis, Darredeau, & Barrett, 2013; Sartor, Kranzler, & Gelernter, 2014b; Trenz et al., 2012); thus, characterization of within-substance progression may not capture important between-substance relationships. One recent study examined between-substance progression in current “hard” (e.g., heroin) substance users and found age at regular use of “soft” (e.g. alcohol, marijuana) substances predicted future “hard” substance use better than age at initial use (Baggio, Studer, Mohler-Kuo, Daeppen, & Gmel, 2013).

Substance-use progression research has also focused on the pattern of between-substance use. The ‘gateway hypothesis’ (Kandel, 1975) postulated two transitions in substance use progression: legal substance use (alcohol, tobacco) preceding marijuana use, and marijuana use preceding “hard” illegal substance use (e.g., cocaine, heroin). The gateway hypothesis implicated initial marijuana use as the critical transition step between legal and “hard” illegal substance use (Kandel, 1975). Experimental evidence for this hypothesis is mixed (Mackesy-Amiti, Fendrich, & Goldstein, 1997) and criticism has generated debate regarding its continued relevance (Golub & Johnson, 2002; Tarter et al., 2012). A novel application of the gateway hypothesis differentiates individuals based on their gateway-pattern agreement

(Tarter, Vanyukov, Kirisci, Reynolds, & Clark, 2006; Wells & McGee, 2008; Agrawal et al., 2011; Sartor, Kranzler, & Gelernter, 2014a). A substance-use progression pattern that is inconsistent with the gateway hypothesis has been associated with environmental factors including: poorer physical environment, greater access to drugs in a neighborhood, and more neglectful parenting (Tarter et al., 2006). In addition, a gateway-inconsistent pattern of progression has been associated with psychiatric dysfunction (DSM-IV diagnoses of internalizing disorders [e.g. depression, anxiety disorders]; Degenhardt et al., 2009; Wells & McGee, 2008) and greater likelihood of progression to substance dependence (Degenhardt et al., 2009; Sartor et al., 2014a).

1.2. Aims and hypotheses

Within a large sample of regular heroin-using, out-of-treatment volunteers, the present study retrospectively examined: (1) age at onset of initial and regular use of tobacco, alcohol, marijuana, and cocaine as predictors of age at onset of regular heroin use; (2) age at regular heroin use as a predictor of current and lifetime heroin use characteristics; and (3) phenotype individuals by agreement (or not) with the gateway pattern of progression. Consistent with recent trends in the literature, we hypothesized that earlier age at onset of regular substance use (as opposed to initial use) would predict earlier regular heroin use. Additionally, we hypothesized that earlier age at onset of regular heroin use and deviating from the gateway pattern of substance use progression would predict heroin use characteristics indicative of a more severe condition.

2. Methods

2.1. Participant selection

Screening data from out-of-treatment, heroin-using adults (18–55 years old) recruited using media advertisements and word-of-mouth referral for several behavioral pharmacology studies (1998–2014) were used in the present analysis. All studies were approved by the local Institutional Review Board and conducted in accordance with the Declaration of Helsinki (1964). Candidates who denied major medical or psychiatric contraindications (e.g., heavy alcohol use, major depression, cardiovascular disease) during the initial structured phone interview were invited to undergo comprehensive in-person screening procedures following written informed consent. Opioid-positive (>300 ng/ml), alcohol-free (<.002%; Alco Sensor III Breathalyzer), and cognitively-intact (IQ score >80; Shipley Institute of Living Scale; Zachary, 1991) individuals were included in the analysis.

2.2. Outcome measures

Lifetime and current substance use characteristics were assessed across five substances (alcohol, tobacco, marijuana, cocaine, and heroin) via a standardized, self-report battery: Drug History and Use Questionnaire (created in our laboratory; available upon request). Age at initial use of a substance is defined as age at first consumption, whereas age at regular use is defined as age when first using at least 3 times per week. Lifetime heroin-use consequences were assessed via an 18-item checklist of items (e.g., overdose, financial problems) not biased by age-specific consequences (problems in school, high at school, and missed school; Woodcock, Lundahl, Burmeister, & Greenwald, in press). Given that one

focus of the present investigation is to explore the effects of age at onset with current and lifetime heroin use characteristics, these age-specific items were excluded to prevent biasing the analysis. Participants indicated (ever/never) each consequence they experienced as a direct result of heroin use in their lifetime. Summed number of items endorsed yielded a total score for analysis (range 0–18). Lifetime consequences for the other substances examined herein were also assessed and computed using similar scales specific to each substance (alcohol: 20 items; tobacco: 16 items; marijuana: 22 items; and cocaine: 18 items). Self-reported lifetime number of attempts to stop using heroin was assessed via a single item score (maximum: 100). Past-month heroin use frequency was calculated as the product of mean daily past-week heroin use and number of past-month days using heroin (maximum: 30 days). Duration of regular heroin use was calculated as age at screening *minus* age at regular heroin use. Each participant's pattern of substance use progression was evaluated for gateway hypothesis agreement. Deviation from the gateway hypothesis was operationally defined as:

1. use of marijuana prior to legal substances (tobacco and alcohol); or
2. use of cocaine or heroin prior to marijuana; or
3. use of cocaine or heroin prior to legal substances (tobacco and alcohol).

Temporal measurement sensitivity was limited, as participants were asked to describe age of initial substance use in calendar-year format. Thus, to qualify as gateway-inconsistent, violators would need to report use of a substance one calendar year out of order (e.g., initial marijuana use at age 12, and tobacco and alcohol use at age 13 or later).

2.3. Data analyses

Variables were assessed for normality (West et al., 1995) and outliers (z-scores ≥ 3.3). Non-normally distributed variables were transformed ($\log_{10}$ or square root) and outliers omitted. Substance use data were characterized using descriptive statistics, frequencies, and one-way analyses of variance (ANOVA). To protect against Type I error inflation due to unequal sample sizes, Levene's Test of Equality of Error Variances was used to confirm ($p > .05$) homogeneity of variance for each outcome variable examined for group differences. Any substance-use measures (e.g., quit attempts) that correlated with duration of use (which could bias interpretation of results) were evaluated using analyses of covariance (ANCOVA) with heroin use duration entered as a covariate. Ordinal tertiles of substance use onset age were created to examine the effect of onset age on other outcome variables.

Predicted outcome variables were analyzed using stepwise linear regression models (pairwise case exclusion). Multi-collinearity was assessed for each regression model and tolerance did not exceed 0.99. Durbin–Watson statistic indicated the independence of errors ($1.5 \leq d \leq 2.5$) for each regression model. Descriptive statistics are presented as mean (M) ± one standard deviation (SD). Analyses were conducted using SPSS version 22 and criterion to reject the null hypothesis was set at $p < .05$.

3. Results

3.1. Demographic characteristics

Data from 562 participants were included in the present analyses. The mean study participant was a 42.4 ± 9.4 year-old African-American (59.6%) male (70.1%) with 12.3 ± 1.6 years of education.

3.2. Substance use characteristics

Substances first used by participants were alcohol (26.3%), tobacco (17.4%), marijuana (11.9%) or a combination thereof (32.8%), which accounted for 88.4% of substances first used (Fig. 1). Examining each substance individually, participants reported initiating alcohol use first (mean age at onset: 14.8 ± 4.9), followed shortly thereafter by marijuana (15.0 ± 3.4) and tobacco (15.7 ± 5.0), with a longer delay until initial cocaine and heroin uses (24.7 ± 7.8 and 23.4 ± 7.8; respectively) (Table 1). In contrast, participants reported regular use of marijuana (16.3 ± 3.5) before tobacco (17.6 ± 5.1) and alcohol (19.2 ± 5.6) with a longer delay until regular use of heroin (25.6 ± 8.1) and cocaine (27.8 ± 8.5). Mean latency between initial and regular use was the shortest for marijuana (1.7 years) and the longest for alcohol (4.9 years). Across the five substances surveyed, participants reported using 2.3 ± 1.2 substances (in addition to heroin) during the past month. Lifetime incidence of use was high across all five substances (range: 91.1–100.0%).

3.3. Progression to regular heroin use

The first stepwise linear regression model examined age at initial use of each non-heroin substance (tobacco, alcohol, marijuana, and cocaine) predicting age at regular heroin use. Earlier onset of initial tobacco and cocaine use (zero-order correlations [r_0] = .19 and .15; βs = .16 and .11, respectively) predicted earlier onset of regular heroin use, $F(2,398) = 9.70$, $p < .001$, and accounted for 4.7% of the total variance (3.6% and 1.1%, respectively).

The second stepwise linear regression model examined age at regular use of each non-heroin substance predicting age at regular heroin use. Earlier onset of regular alcohol and tobacco use (r_0 = .25 and .21; βs = .20 and .14, respectively) predicted earlier onset of regular heroin use, $F(2,223) = 9.68$, $p < .001$, and accounted for 8.1% of the total variance (6.2% and 1.8%, respectively).

The third stepwise linear regression model examined the significant predictors from the first two models and age at regular heroin use. Results were unchanged from the second regression model: age at regular alcohol and tobacco use predicted earlier onset of regular heroin use (r_0 = .25 and .21; βs = .20 and .14, respectively), accounting for 8.1% of the total variance, $F(2,283) = 12.31$; $p < .001$. Further examination of age at regular alcohol use revealed those who initiated regular use younger (earlier tertile; aged 8–16 years; $n = 115$; 31.1%) progressed to regular heroin use more than four years earlier (23.9 ± 7.9 vs. 28.5 ± 8.4) than those who initiated regular alcohol use later (later tertile; aged 20+ years; n = 135; 36.5%) (Fig. 2). Similarly, those who reported younger age at regular tobacco use (aged 8–15 years; $n = 152$; 34.1%) progressed to regular heroin use more than four years younger

(23.8 ± 7.9 vs. 28.3 ± 8.0) than those who initiated regular tobacco use later (aged 19+ years; $n = 118$; 26.5%) (Fig. 3).

The final stepwise linear regression model included age at initial heroin use, in addition to the significant predictors from the third model, predicting age at regular heroin use. As expected, earlier initial heroin use predicted earlier regular heroin use ($r_0 = .85$) and accounted for 71.8% of the total variance, $F(1,283) = 718.53$; $\beta = .85$, $p < .001$. Indeed, half the sample progressed from initial to regular heroin use within the same calendar year ($n = 277$; 49.3%), and more than three-quarters progressed to regular heroin use within their first two years of heroin use ($n = 428$; 76.2%). Unexpectedly, age at regular alcohol use also significantly predicted age at regular heroin use, $F(2,283) = 371.11$; $p < .001$, but only accounted for 0.7% of the variance ($r_0 = .25$; $\beta = .09$).

3.4. Relevance of regular heroin use onset

Participants who reported earlier onset of regular heroin use (earlier tertile; aged 9–20 years; $n = 187$; 33.3%) progressed from initial to regular use more quickly [$F(2,561) = 10.33$; $p < .001$; 1.0 ± 1.4 vs. 3.8 ± 6.6 years], and reported a longer duration of heroin use [$F(2,561) = 111.11$; $p < .001$; 24.5 ± 11.8 vs. 9.8 ± 5.6 years] than those who began regular heroin use later (later tertile; aged 30+ years; $n = 182$; 32.4%). Age at regular heroin use onset was examined as a predictor of heroin use-related consequences, quit attempts, route of administration, and past-month use frequency. Bivariate correlation analyses indicated that heroin use duration was significantly correlated with quit attempts ($r = .14$; $p < .001$) and past-month use frequency ($r = -.10$; $p < .05$), but not consequences ($p = .84$). One-way ANOVA revealed earlier onset of regular heroin use (tertile values) was associated with more lifetime heroin use-related consequences [$F(2,586) = 9.65$; $p < .001$; 7.9 ± 4.5 vs. 6.1 ± 4.1]. Earlier onset of regular heroin use (tertile values) was associated with increased likelihood to administer heroin via injection (vs. smoking/snorting) [$\chi^2(2) = 18.25$; $p < .001$; 36.8% vs. 26.4%]. Controlling for heroin use duration, earlier onset of regular heroin use was not associated with more frequent past-month heroin use ($p = .10$) or number of lifetime heroin quit attempts ($p = .98$).

3.5. Gateway hypothesis

The majority of this sample ($n = 401$; 79.7%) reported drug-use progression consistent with the gateway hypothesis. Gateway-consistent progression was heterogeneous (Fig. 4), such that participants more frequently initiated marijuana use in combination with tobacco and/or alcohol (in the same calendar year; $n = 204$; 50.9%) than progressed serially from alcohol or tobacco to marijuana use ($n = 149$; 37.2%). Participants were more likely to progress from marijuana use to either heroin or cocaine use ($n = 154$ vs. 153) than to both heroin and cocaine use in the same year ($n = 47$; 11.7%). Those who initiated marijuana in combination with tobacco and/or alcohol, and heroin in combination with cocaine, reported being younger at onset than those who progressed serially (marijuana: 14.4 vs. 15.3 years; and heroin: 23.1 vs. 25.0 years).

Gateway-pattern violations were mostly attributed to marijuana use prior to alcohol/tobacco (67.7%) or cocaine/heroin use prior to marijuana use (29.0%). A small subset of participants

violated multiple gateway transitions ($n = 15$). Gateway-inconsistent participants were older at screening, initiated heroin use younger, and were more likely to be African-American than gateway-consistent participants (Table 2). Controlling for heroin use duration, gateway-inconsistent participants reported more past-month heroin use. Participant age at screening was correlated with heroin use duration ($r = .71$; $p < .001$). Controlling for participant age, gateway-inconsistent participants reported more years of heroin use. No other heroin use characteristics were related to participant's gateway progression pattern ($p > .05$).

4. Discussion

The present study retrospectively examined the chronology of substance-use progression and clinically-relevant outcomes in out-of-treatment, chronic heroin users. Results indicated age at initial heroin use was the strongest predictor and accounted for nearly three-quarters of the variance in age at regular heroin use. Earlier onset of regular alcohol and tobacco use also significantly predicted earlier onset of regular heroin use. Earlier onset of regular heroin use was associated with faster progression from initial to regular use, longer heroin use duration, more heroin use consequences, and greater likelihood of injecting heroin. The majority of participants progressed in a pattern consistent with the gateway hypothesis. However, gateway-inconsistent individuals initiated heroin use younger, reported longer heroin use duration, and more frequent past-month heroin use than gateway-consistent individuals. Additionally, gateway-inconsistent individuals were older at screening and more likely to report being African-American. These findings demonstrated that substance use chronology predicted progression to regular heroin use and age at onset of regular heroin use predicted clinically-relevant heroin use characteristics in out-of-treatment heroin users. Additionally, gateway pattern agreement may provide valuable heroin-use subtyping information.

4.1. Progression to regular heroin use

The present study examined predictors of age at regular heroin use onset, as opposed to age at initial use, for two reasons: 1) recent conceptualizations (Baggio et al., 2013; Kuntsche et al., 2013) and 2) the hypothesized proximity to the transition from presumably impulsive (or opportunistic) experimentation to compulsive, regular substance use (Kreek, Nielsen, Butelman, & LaForge, 2005; Storr, Westergaard, & Anthony, 2005). Similar to Baggio et al. (2013), we found earlier regular use of alcohol and tobacco predicted earlier onset of regular heroin use more accurately than initial use of any non-heroin substance examined. Results indicated those who regularly used tobacco by age 15 and alcohol by age 16 progressed to regular heroin use four years younger compared to those who regularly used tobacco and alcohol at ages 19 and age 20 or older, respectively. As hypothesized, the strongest predictor of regular heroin use was age at initial heroin use, accounting for 71.8% of the variance. Half of the sample progressed to regular heroin use in the same calendar year they initiated heroin use. Clinical studies demonstrate those who were older at substance use initiation and reported longer latency to dependence experienced better treatment outcomes (Ellickson et al., 2004). These findings highlight the importance of early intervention.

4.2. Relevance of regular heroin use onset

Earlier onset of regular heroin use was associated with more rapid progression from initial to regular use, longer duration of heroin use, more heroin use-related consequences, and greater likelihood of administering heroin via injection. The present findings are consistent with Chen et al. (2011) who found earlier onset was associated with greater symptom severity in alcohol dependent individuals. Earlier-onset regular users reported more than twice longer heroin use duration (24.5 vs. 9.8 years) and nearly four times faster progression from initial to regular use (1.0 vs. 3.8 years) compared to later-onset regular users. Those who progressed at a younger age reported experiencing two more heroin use-related consequences; which is indicative of greater overall socio-behavioral dysfunction. Finally, earlier-onset regular users reported greater likelihood of injecting heroin, which prior studies demonstrated was associated with increased risk of contracting blood-borne diseases (e.g., HIV), medical consequences (e.g., collapsed veins) (Chitwood et al., 2003; UNODC, 2013) and, in treatment-seeking individuals, worse clinical outcomes (Subramaniam et al., 2011). Taken together, these results indicate the trajectory of heroin use significantly influences current heroin use characteristics that are associated with a more burdensome disorder and worse treatment outcomes.

4.3. Gateway hypothesis

Marijuana's legal status is evolving in the United States, which complicates the already controversial gateway theory (Kandel, 1975). The majority (79.7%) of this sample progressed in a pattern that was consistent with the gateway hypothesis. Interestingly, more individuals initiated marijuana use in combination (in the same calendar year) with tobacco and/or alcohol than progressed serially from alcohol and/or tobacco to marijuana use. Participants who reported poly-substance initiation were younger at substance use onset than those who progressed serially. The percentage of gateway-inconsistent individuals in our study is consistent with one report (Tarter et al., 2006), but significantly higher than others (Degenhardt et al., 2009; Sartor et al., 2014a; Wells & McGee, 2008). These discrepant findings could be explained by methodological differences between study samples (nationally-representative and multi-site vs. neighborhood and out-of-treatment). Others have demonstrated participant characteristics differed by gateway-consistent vs. inconsistent groups (Agrawal et al., 2011; Degenhardt et al., 2009; Sartor et al., 2014a). The present findings indicated gateway-inconsistent individuals were more likely to be African-American and older at screening. The earlier finding is consistent with previous studies and may reflect sociocultural differences or substance-use opportunities (Sartor et al., 2013; Sartor et al., 2014a; White, Jarrett, Valencia, Loeber, & Wei, 2007). In the present study, gateway-inconsistent individuals were younger at initial (but not regular) heroin use, reported a longer duration of heroin use (controlling for age at screening), and more frequent past-month heroin use. Unlike other studies (Degenhardt et al., 2009; Sartor et al., 2014a), our findings indicate that 'out-of-sequence' substance use was associated with heroin use characteristics (earlier onset, longer duration and more frequent use) that, in treatment studies, predicted worse outcomes (Hillhouse, Canamar, & Ling, 2013; Soyka, Zingg, Koller, & Kuefner, 2008; Warden et al., 2012; Ziedonis et al., 2009).

4.4. Limitations

Several limitations of the present study should be mentioned. First, potential biases inherent in self-reported retrospective substance use history data make it difficult to disentangle the exact temporal sequence of poly-substance use (Johnson & Schultz, 2005). Second, the present data were limited in their temporal precision (calendar year), which led to conservative assignment of gateway-inconsistent progression. Third, we were not able to address other prominent theories of substance use progression, including work by Anthony and colleagues examining the importance of exposure opportunities (Anthony, 2002; Wagner & Anthony, 2002; Wilcox, Wagner, & Anthony, 2002), and Vanyukov and colleagues investigating common liability to addiction (Vanyukov et al., 2003, 2009, 2012). Fourth, this study excluded individuals with serious psychiatric conditions (e.g. current major depression, anxiety disorders or schizophrenia) and thus, limited our ability to examine the association between substance use progression and psychiatric disorders. Finally, the present study did not consider cultural or parental factors, environmental stressors, genetic polymorphisms or personality attributes (Brook, Morojele, Pahl, & Brook, 2006) that may have influenced the observed effects and represent important considerations for future research.

4.5. Conclusion

In conclusion, this study examined two prominent models of substance use progression in an under-studied population: out-of-treatment, chronic heroin users. Age at regular alcohol and tobacco use were the strongest between-substance predictors of age at regular heroin use. Ultimately, age at initial heroin use was the best overall predictor of age at regular heroin use. Earlier onset of regular heroin use was associated with variables consistent with a more burdensome and treatment non-responsive disorder, including: more rapid progression from initial to regular use, longer duration of heroin use, more use-related consequences and greater likelihood of injecting heroin. Finally, the majority of the sample progressed in a pattern consistent with the gateway hypothesis. Gateway-inconsistent individuals were more likely to be African-American, initiate heroin use younger and use longer, and report more frequent past-month heroin use. Our findings demonstrate the predictive validity and clinical relevance of substance use chronology and gateway sequence evaluation.

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References

Agrawal A, Scherrer JF, Lynskey MT, Sartor CE, Grant JD, Haber JR, et al. Patterns of use, sequence of onsets and correlates of tobacco and cannabis. Addictive Behaviors. 2011; 36(12):1141–1147. http://dx.doi.org/10.1016/j.addbeh.2011.07.005. [PubMed: 21820810]

Anthony JC. Death of the 'stepping-stone' hypothesis and the 'gateway' model? Comments on Morral et al. Addiction. 2002; 97(12):1505–1507.

Baggio S, Studer J, Mohler-Kuo M, Daeppen JB, Gmel G. Profiles of drug users in Switzerland and effects of early-onset intensive use of alcohol, tobacco and cannabis on other illicit drug use. Swiss Medical Weekly. 2013; 143:w13805. http://dx.doi.org/10.4414/smw.2013.13805. [PubMed: 23740102]

Breslau N, Fenn N, Peterson EL. Early smoking initiation and nicotine dependence in a cohort of young adults. Drug and Alcohol Dependence. 1993; 33(2):129–137. http://dx.doi.org/10.1016/0376-8716(93)90054-T. [PubMed: 8261877]

Brook DW, Brook JS, Zhang C, Cohen P, Whiteman M. Drug use and the risk of major depressive disorder, alcohol dependence, and substance use disorders. Archives of General Psychiatry. 2002; 59(11):1039–1044. http://dx.doi.org/10.1001/archpsyc.59.11.1039. [PubMed: 12418937]

Brook JS, Morojele NK, Pahl K, Brook DW. Predictors of drug use among South African adolescents. The Journal of Adolescent Health. 2006; 38(1):26–34. http://dx.doi.org/10.1016/j.jadohealth.2004.08.004. [PubMed: 16387245]

Chen CY, O'Brien MS, Anthony JC. Who becomes cannabis dependent soon after onset of use? Epidemiological evidence from the United States: 2000–2001. Drug and Alcohol Dependence. 2005; 79(1):11–22. http://dx.doi.org/10.1016/j.drugalcdep.2004.11.014. [PubMed: 15943940]

Chen CY, Storr CL, Anthony JC. Early-onset drug use and risk for drug dependence problems. Addictive Behaviors. 2009; 34(3):319–322. http://dx.doi.org/10.1016/j.addbeh.2008.10.021. [PubMed: 19022584]

Chen YC, Prescott CA, Walsh D, Patterson DG, Riley BP, Kendler KS, et al. Different phenotypic and genotypic presentations in alcohol dependence: age at onset matters. Journal of Studies on Alcohol and Drugs. 2011; 72(5):752–762. [PubMed: 21906503]

Chitwood DD, Comerford M, Sanchez J. Prevalence and risk factors for HIV among sniffers, short-term injectors, and long-term injectors of heroin. Journal of Psychoactive Drugs. 2003; 35(4):445–453. http://dx.doi.org/10.1080/02791072.2003.10400491. [PubMed: 14986873]

Degenhardt L, Chiu WT, Conway K, Dierker L, Glantz M, Kalaydjian A, et al. Does the 'gateway' matter? Associations between the order of drug use initiation and the development of drug dependence in the National Comorbidity Study Replication. Psychological Medicine. 2009; 39(1):157–167. http://dx.doi.org/10.1017/S0033291708003425. [PubMed: 18466664]

DeWit DJ, Adlaf EM, Offord DR, Ogborne AC. Age at first alcohol use: A risk factor for the development of alcohol disorders. The American Journal of Psychiatry. 2000; 157(5):745–750. [PubMed: 10784467]

Ellickson PL, Martino SC, Collins RL. Marijuana use from adolescence to young adulthood: Multiple developmental trajectories and their associated outcomes. Health Psychology. 2004; 23(3):299–307. http://dx.doi.org/10.1037/0278-6133.23.3.299. [PubMed: 15099171]

Golub A, Johnson BD. The misuse of the 'Gateway Theory' in US policy on drug abuse control: A secondary analysis of the muddled deduction. The International Journal on Drug Policy. 2002; 13(1):5–19. http://dx.doi.org/10.1016/S0955-3959(01)00111-6.

Grant BF, Dawson DA. Age at onset of alcohol use and its association with DSM-IV alcohol abuse and dependence: Results from the national longitudinal alcohol epidemiologic survey. Journal of Substance Abuse. 1997; 9:103–110. http://dx.doi.org/10.1016/S0899-3289(97)90009-2. [PubMed: 9494942]

Grant BF, Stinson FS, Harford TC. Age at onset of alcohol use and DSM-IV alcohol abuse and dependence: A 12-year follow-up. Journal of Substance Abuse. 2001; 13(4):493–504. http://dx.doi.org/10.1016/S0899-3289(01)00096-7. [PubMed: 11775078]

Hillhouse M, Canamar CP, Ling W. Predictors of outcome after short-term stabilization with buprenorphine. Journal of Substance Abuse Treatment. 2013; 44(3):336–342. http://dx.doi.org/10.1016/j.jsat.2012.08.016. [PubMed: 23021099]

Hser YI, Longshore D, Anglin MD. The life course perspective on drug use: A conceptual framework for understanding drug use trajectories. Evaluation Review. 2007; 31(6):515–547. http://dx.doi.org/10.1177/0193841x07307316. [PubMed: 17986706]

Hu MC, Griesler PC, Schaffran C, Wall MM, Kandel DB. Trajectories of criteria of nicotine dependence from adolescence to early adulthood. Drug and Alcohol Dependence. 2012; 125(3): 283–289. http://dx.doi.org/10.1016/j.drugalcdep.2012.03.001. [PubMed: 22513378]

Johnson EO, Schultz L. Forward telescoping bias in reported age of onset: An example from cigarette smoking. International Journal of Methods in Psychiatric Research. 2005; 14(3):119–129. http://dx.doi.org/10.1002/mpr.2. [PubMed: 16389888]

Kandel D. Stages in adolescent involvement in drug use. Science. 1975; 190(4217):912–914. http://dx.doi.org/10.1126/science.1188374. [PubMed: 1188374]

Kreek MJ, Nielsen DA, Butelman ER, LaForge KS. Genetic influences on impulsivity, risk taking, stress responsivity and vulnerability to drug abuse and addiction. Nature Neuroscience. 2005; 8(11):1450–1457. http://dx.doi.org/10.1038/nn1583. [PubMed: 16251987]

Kuntsche E, Rossow I, Simons-Morton B, Bogt TT, Kokkevi A, Godeau E. Not early drinking but early drunkenness is a risk factor for problem behaviors among adolescents from 38 European and North American countries. Alcoholism: Clinical and Experimental Research. 2013; 37(2):308–314. http://dx.doi.org/10.1111/j.1530-0277.2012.01895.x.

Lee CY, Winters KC, Wall MM. Trajectories of substance use disorders in youth: Identifying and predicting group memberships. Journal of Child & Adolescent Substance Abuse. 2010; 19(2):135–157. http://dx.doi.org/10.1080/10678281003634975. [PubMed: 20485542]

Mackesy-Amiti ME, Fendrich M, Goldstein PJ. Sequence of drug use among serious drug users: Typical vs atypical progression. Drug and Alcohol Dependence. 1997; 45(3):185–196. http://dx.doi.org/10.1016/S0376-8716(97)00032-X. [PubMed: 9179520]

Moss HB, Chen CM, Yi HY. Early adolescent patterns of alcohol, cigarettes, and marijuana polysubstance use and young adult substance use outcomes in a nationally representative sample. Drug and Alcohol Dependence. 2013; 136:51–62. http://dx.doi.org/10.1016/j.drugalcdep.2013.12.011. [PubMed: 24434016]

Nelson CB, Wittchen HU. DSM-IV alcohol disorders in a general population sample of adolescents and young adults. Addiction. 1998; 93(7):1065–1077. http://dx.doi.org/10.1046/j.1360-0443.1998.937106511.x. [PubMed: 9744137]

Olthuis JV, Darredeau C, Barrett SP. Substance use initiation: The role of simultaneous polysubstance use. Drug and Alcohol Review. 2013; 32(1):67–71. http://dx.doi.org/10.1111/j.1465-3362.2012.00470.x. [PubMed: 22612987]

SAMHSA. Results from the 2012 national survey on drug use and health: Summary of national findings. 2013. NSDUH series H-46, HHS publication no. (SMA), 13-4795

Sartor CC, Agrawal A, Lynskey MT, Duncan AE, Grant JD, Nelson EC, et al. Cannabis or alcohol first? Differences by ethnicity and in risk for rapid progression to cannabis-related problems in women. Psychological Medicine. 2013; 43(04):813–823. http://dx.doi.org/10.1017/S0033291712001493. [PubMed: 22804877]

Sartor CE, Kranzler HR, Gelernter J. Characteristics and course of dependence in cocaine-dependent individuals who never used alcohol or marijuana or used cocaine first. Journal of Studies on Alcohol and Drugs. 2014a; 75(3):423–427. [PubMed: 24766754]

Sartor CE, Kranzler HR, Gelernter J. Rate of progression from first use to dependence on cocaine or opioids: A cross-substance examination of associated demographic, psychiatric, and childhood risk factors. Addictive Behaviors. 2014b; 39(2):473–479. http://dx.doi.org/10.1016/j.addbeh.2013.10.021. [PubMed: 24238782]

Soyka M, Zingg C, Koller G, Kuefner H. Retention rate and substance use in methadone and buprenorphine maintenance therapy and predictors of outcome: Results from a randomized study. The International Journal of Neuropsychopharmacology. 2008; 11(5):641–653. http://dx.doi.org/10.1017/S146114570700836X. [PubMed: 18205978]

Storr CL, Westergaard R, Anthony JC. Early onset inhalant use and risk for opiate initiation by young adulthood. Drug and Alcohol Dependence. 2005; 78(3):253–261. http://dx.doi.org/10.1016/j.drugalcdep.2004.11.005. [PubMed: 15893156]

Subramaniam GA, Warden D, Minhajuddin A, Fishman MJ, Stitzer ML, Adinoff B, et al. Predictors of abstinence: National Institute of Drug Abuse multisite buprenorphine/naloxone treatment trial in opioid-dependent youth. Journal of the American Academy of Child and Adolescent Psychiatry. 2011; 50(11):1120–1128. http://dx.doi.org/10.1016/j.jaac.2011.07.010. [PubMed: 22024000]

Tarter RE, Kirisci L, Mezzich A, Ridenour T, Fishbein D, Horner M, et al. Does the "gateway" sequence increase prediction of cannabis use disorder development beyond deviant socialization? Implications for prevention practice and policy. Drug and Alcohol Dependence. 2012; 123(Supplement 1)(0):S72–S78. http://dx.doi.org/10.1016/j.drugalcdep.2012.01.015. [PubMed: 22365896]

Tarter RE, Vanyukov M, Kirisci L, Reynolds M, Clark DB. Predictors of marijuana use in adolescents before and after licit drug use: Examination of the gateway hypothesis. The American Journal of Psychiatry. 2006; 163(12):2134–2140. [PubMed: 17151165]

Trenz RC, Scherer M, Harrell P, Zur J, Sinha A, Latimer W. Early onset of drug and polysubstance use as predictors of injection drug use among adult drug users. Addictive Behaviors. 2012; 37(4):367–372. http://dx.doi.org/10.1016/j.addbeh.2011.11.011. [PubMed: 22172686]

United Nations Office on Drugs and Crime (UNODC). World drug report. United Nations Publication; 2013. at: http://docsize.com/files/world-drug-report-2013-united-nations-office-on-drugs-and-crime.html [Accessed 1-14-15]

Vanyukov MM, Kirisci L, Moss L, Tarter RE, Reynolds MD, Maher BS, et al. Measurement of the risk for substance use disorders: Phenotypic and genetic analysis of an index of common liability. Behavior Genetics. 2009; 39(3):233–244. http://dx.doi.org/10.1007/s10519-009-9269-9. [PubMed: 19377872]

Vanyukov MM, Tarter RE, Kirillova GP, Kirisci L, Reynolds MD, Kreek MJ, et al. Common liability to addiction and "gateway hypothesis": Theoretical, empirical and evolutionary perspective. Drug and Alcohol Dependence. 2012; 123(Suppl 1):S3–S17. http://dx.doi.org/10.1016/j.drugalcdep.2011.12.018. [PubMed: 22261179]

Vanyukov MM, Tarter RE, Kirisci L, Kirillova GP, Maher BS, Clark DB. Liability to substance use disorders: 1. Common mechanisms and manifestations. Neuroscience & Biobehavioral Reviews. 2003; 27(6):507–515. http://dx.doi.org/10.1016/j.neubiorev.2003.08.002. [PubMed: 14599432]

Wagner FA, Anthony JC. Into the world of illegal drug use: Exposure opportunity and other mechanisms linking the use of alcohol, tobacco, marijuana, and cocaine. American Journal of Epidemiology. 2002; 155(10):918–925. [PubMed: 11994231]

Warden D, Subramaniam GA, Carmody T, Woody GE, Minhajuddin A, Poole SA, et al. Predictors of attrition with buprenorphine/naloxone treatment in opioid dependent youth. Addictive Behaviors. 2012; 37(9):1046–1053. http://dx.doi.org/10.1016/j.addbeh.2012.04.011. [PubMed: 22626890]

Wells JE, McGee MA. Violations of the usual sequence of drug initiation: Prevalence and associations with the development of dependence in the New Zealand Mental Health Survey. Journal of Studies on Alcohol and Drugs. 2008; 69:789–795. [PubMed: 18925336]

West, SG., Finch, JF., Curran, PJ. Structural equation models with nonnormal variables: Problems and remedies. In: Hoyle, RH., editor. Structural equation modeling: Concepts, issues, and applications. CA: Newberry Park; 1995. p. 56-75.

White HR, Jarrett N, Valencia EY, Loeber R, Wei E. Stages and sequences of initiation and regular substance use in a longitudinal cohort of black and white male adolescents. Journal of Studies on Alcohol and Drugs. 2007; 68(2):173–181. [PubMed: 17286335]

Wilcox HC, Wagner FA, Anthony JC. Exposure opportunity as a mechanism linking youth marijuana use to hallucinogen use. Drug and Alcohol Dependence. 2002; 66(2):127–135. http://dx.doi.org/10.1016/S0376-8716(01)00191-0. [PubMed: 11906800]

Windle M, Windle RC. Early onset problem behaviors and alcohol, tobacco, and other substance use disorders in young adulthood. Drug and Alcohol Dependence. 2012; 121(1–2):152–158. http://dx.doi.org/10.1016/j.drugalcdep.2011.08.024. [PubMed: 21925804]

Woodcock EA, Lundahl LH, Burmeister M, Greenwald MK. Functional mu opioid receptor polymorphism (OPRM1 A118G) associated with heroin use outcomes in Caucasian males: A pilot study. The American Journal on Addictions. 2015s (in press).

Zachary, RA. Shipley Institute of Living Scale: revised manual. Los Angeles: Western Psychological Services; 1991.

Ziedonis DM, Amass L, Steinberg M, Woody G, Krejci J, Annon JJ, et al. Predictors of outcome for short-term medically supervised opioid withdrawal during a randomized, multicenter trial of buprenorphine-naloxone and clonidine in the NIDA clinical trials network drug and alcohol dependence. Drug and Alcohol Dependence. 2009; 99(1–3):28–36. http://dx.doi.org/10.1016/j.drugalcdep.2008.06.016. [PubMed: 18805656]

HIGHLIGHTS

- Strongest predictor of earlier regular heroin use was earlier initial heroin use.
- Earlier-onset regular alcohol and tobacco use predicted earlier regular heroin use.
- Earlier regular heroin use was associated with more severe heroin use characteristics.
- Most subjects reported substance progression consistent with the gateway hypothesis.
- Gateway-inconsistent progression was associated with heroin use characteristics.

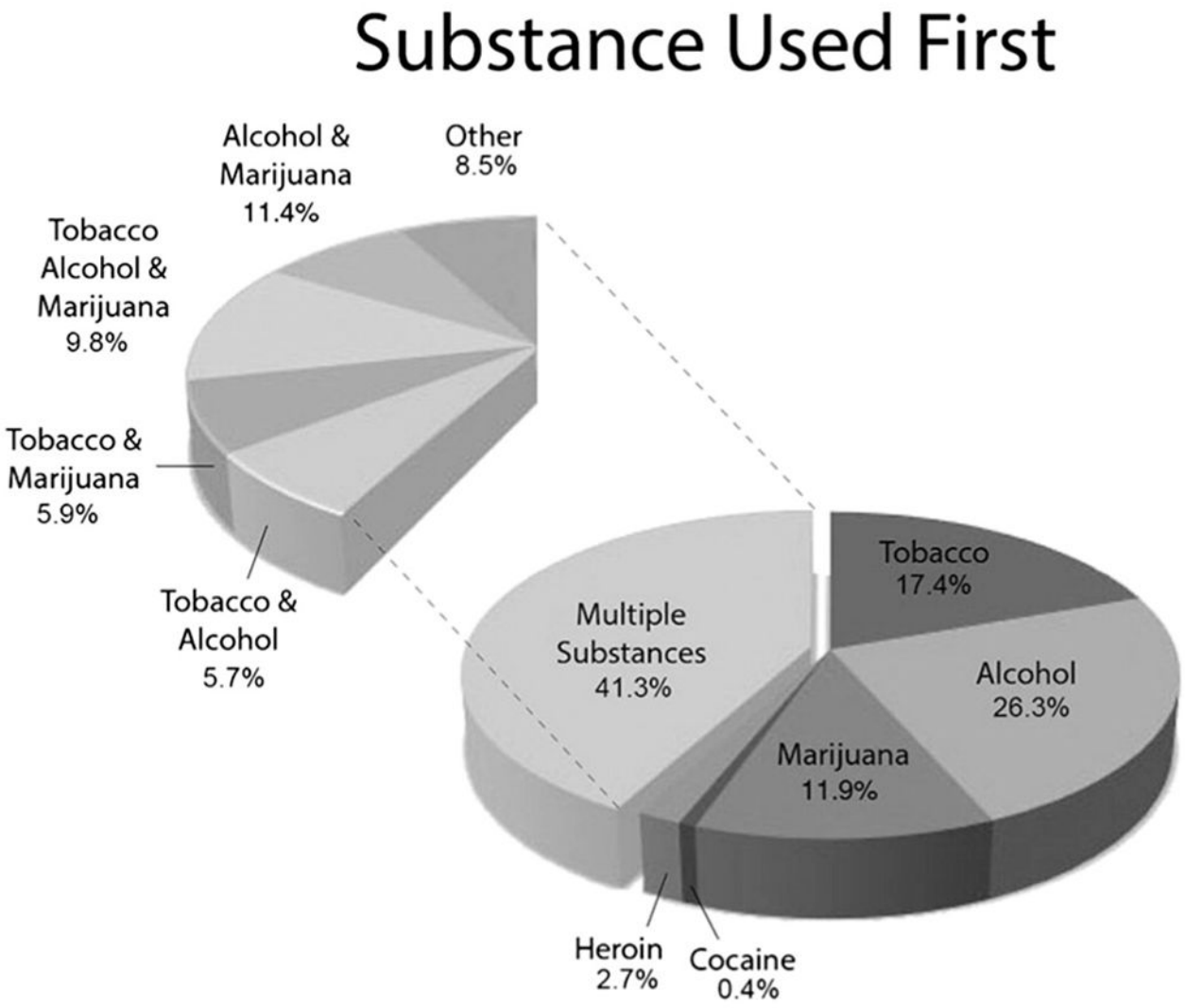

Fig. 1.

Initial substance consumption is characterized (% of sample; $N = 562$) by substance(s) used first across participants.

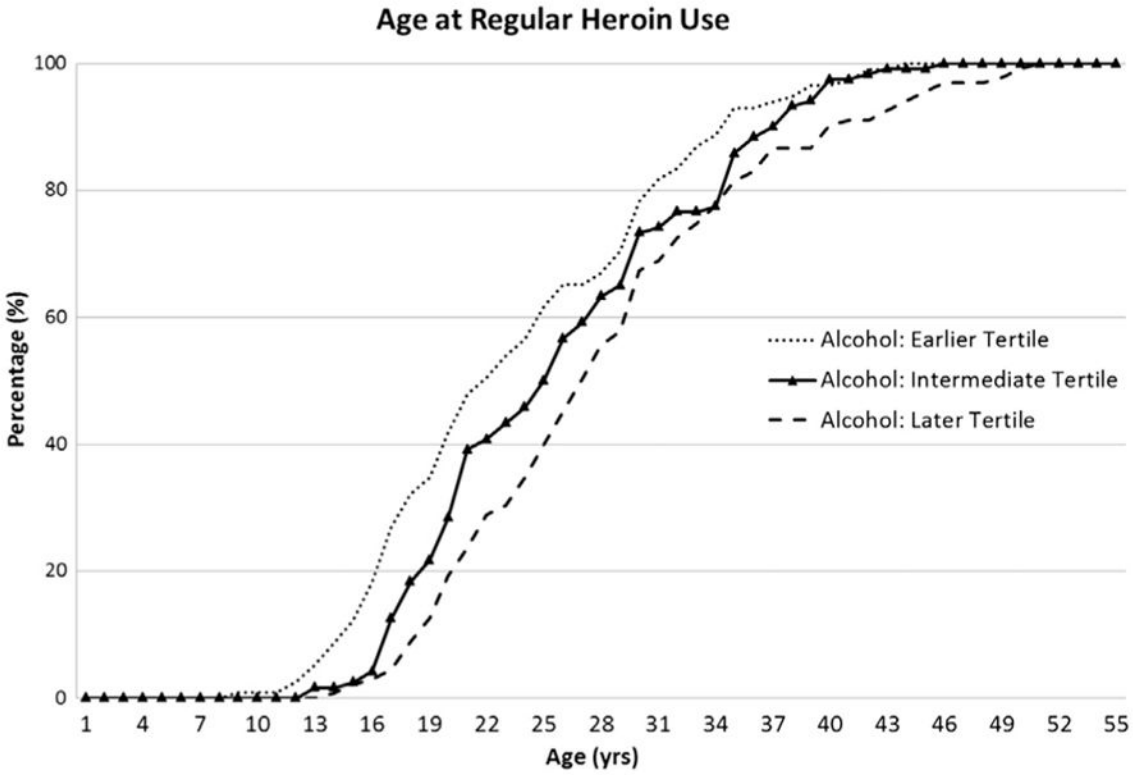

Fig. 2.

Age at onset of regular heroin use (≥3 uses per week) is depicted as a function of age at onset of regular alcohol use (≥3 uses per week). Percentage of each tertile of age at onset of regular alcohol use (earlier [8–16 years], intermediate [17–19 years], and later [20+ years]) is plotted on the y-axis and considered chronologically by age (years) at onset of regular heroin use (x-axis).

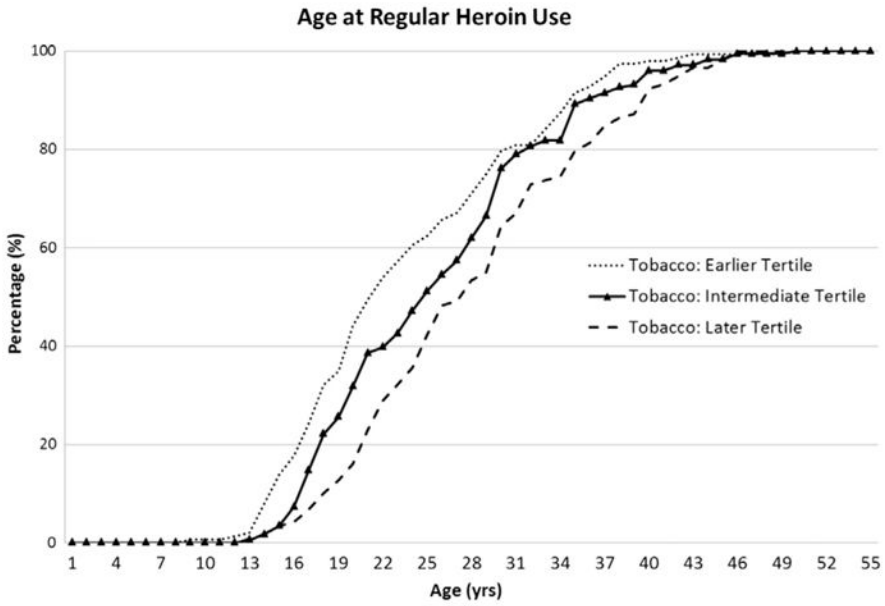

Fig. 3.

Age at onset of regular heroin use (≥3 uses per week) is depicted as a function of age at onset of regular tobacco use (≥3 uses per week). Percentage of each tertile of age at onset of regular tobacco use (earlier [8–15 years], intermediate [16–18 years], and later [19+ years]) is plotted on the y-axis and considered chronologically by age (years) at onset of regular heroin use (x-axis).

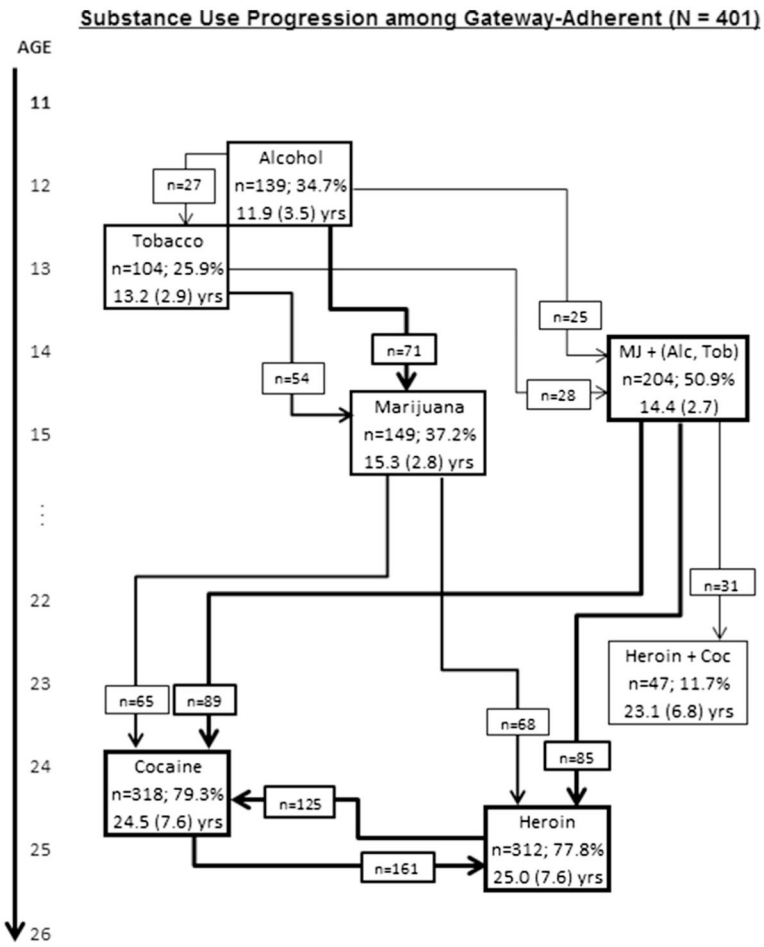

Fig. 4.

Substance use progression among gateway-consistent individuals ($n = 401$) is plotted by age at onset. Each substance displayed in its own node (box) indicates that substance was used in temporal isolation (participant reported only the one substance initiated in that calendar year). Mean age at onset for each substance or combination of substances is depicted M (±1 SD). Percentages displayed are the proportion of gateway-consistent individuals. More common pathways and nodes are bolded for emphasis. To reduce complexity, less populated nodes and minor pathways of drug progression ($n \leq 25$) were omitted, and thus pathways and nodes will not sum to 100% of the sample.

Table 1

Substance use characteristics.

	Tobacco	Alcohol	Marijuana	Cocaine	Heroin
Used in lifetime (%)	97.6%	95.8%	91.4%	91.1%	100.0%
Used regularly in lifetime (%)	79.6%	66.5%	72.3%	56.8%	100.0%
Current user (past month) (%)	96.8%	48.3%	47.3%	65.7%	100.0%
Age at first use	15.7 (5.0)	14.8 (4.9)	15.0 (3.4)	24.7 (7.8)	23.4 (7.8)
Age at regular use	17.6 (5.1)	19.2 (5.6)	16.3 (3.5)	27.8 (8.5)	25.6 (8.1)
Progression to regular use (year)	2.1 (3.1)	4.9 (4.8)	1.7 (2.6)	2.7 (4.4)	2.2 (4.4)
Past month use frequency	441.2 (265.7)	10.3 (25.3)	9.3 (35.1)	51.3 (138.4)	118.8 (105.3)
Lifetime quit attempts	3.5 (9.2)	1.2 (3.1)	1.6 (7.0)	5.1 (13.6)	10.5 (19.1)
Lifetime use consequences	5.1 (4.5)	2.9 (4.2)	2.8 (4.0)	2.9 (3.7)	7.2 (4.4)

Note: Data are presented as mean (±1 standard deviation) unless otherwise specified.

Table 2

Gateway progression pattern.

	Deviant (*n* = 102)	**Adherent (*n* = 401)**	***F* or χ^2**
Demographics			
Age	**44.6 (8.6)**	**41.4 (9.8)**	**9.49**
Gender (% male)	72.5%	70.8%	–
Ethnicity (% African-American)	**74.7%**	**53.1%**	**16.07**
Education (year)	12.3 (1.7)	12.4 (1.6)	–
Heroin use characteristics			
Route of administration (% injection)	66.0%	70.4%	–
Past month use frequency[a]	**137.7 (146.6)**	**114.2 (97.0)**	**5.62**
Lifetime use consequences	6.8 (4.3)	7.6 (4.3)	–
Lifetime quit attempts[a]	13.4 (24.1)	9.9 (17.5)	–
Age at first use	**21.3 (7.7)**	**23.6 (7.5)**	**7.84**
Age at regular use	24.3 (8.1)	25.7 (8.0)	–
Duration (year)[b]	**20.5 (11.2)**	**15.7 (11.1)**	**4.52**

Note: Data are presented as mean (±1 standard deviation) unless otherwise specified. Bold rows indicate significant differences ($p < .05$).

[a]Indicates ANCOVA was used and heroin use duration was entered as a covariate.

[b]Indicates ANCOVA was used and current age was entered as a covariate.