Characteristics and Course of Dependence in Cocaine-Dependent Individuals Who Never Used Alcohol or Marijuana or Used Cocaine First

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ABSTRACT. Objective: Cocaine users typically try alcohol or marijuana before cocaine, but this ordering of substance use initiation is not universal. Characterizing cocaine-dependent users who deviate from the typical sequence may be informative for understanding the multiple pathways to cocaine dependence. **Method:** Data were drawn from cocaine-dependent participants ($N = 6,333$; 41% female) in a multisite study of the genetics of substance dependence who completed in-person structured psychiatric interviews. Participants were categorized with respect to alcohol or marijuana use as (a) never used, (b) used cocaine first, or (c) first used at the same age as or after first cocaine use. The association of a range of demographic, psychiatric, and childhood risk factors with sequences of initiation and the association of those sequences with

indicators of dependence course (e.g., severity) were investigated in a series of regression analyses. **Results:** Women and non-European Americans were overrepresented in the atypical sequence groups. The atypical sequence groups also differed from the typical sequence groups with respect to rates of other substance use disorders. Sequences of substance use initiation were largely unrelated to other psychiatric disorders or childhood risk factors. Individuals who never used marijuana had a lower severity of dependence. **Conclusions:** Although only a minority of dependent cocaine users deviate from the typical sequence of substance use initiation, several characteristics distinguish them from those who follow the typical sequence. Findings underscore the diversity in pathways to cocaine dependence. (*J. Stud. Alcohol Drugs*, 75, 423–427, 2014)

ACCORDING TO THE 2009 National Survey on Drug Use and Health (Substance Abuse and Mental Health Services Administration, 2010), 1.1 million Americans met criteria for cocaine abuse or dependence in the previous 12 months (based on *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)*, criteria; American Psychiatric Association, 1994). The pathway to dependence on “hard drugs” such as cocaine has long been treated as one that nearly universally involves the use of alcohol or cigarettes before marijuana and marijuana before other illicit drugs (Kandel and Faust, 1975). However, the estimated proportion of illicit drug users who follow the typical sequence varies considerably across studies, from as high as 98% to as low as just over 80% (Degenhardt et al., 2009, 2010; Fergusson et al., 2006; Wells and McGee, 2008). The substantial subgroup of drug users who follow alternate sequences may

be highly informative in identifying substance-specific risk factors. The overrepresentation of atypical sequences in certain populations further suggests the value of this line of research for understanding heterogeneity in the development of substance use disorders (SUDs).

Deviations from the typical order of substance use initiation are more common in African Americans than European Americans (Ellickson et al., 1992; Sartor et al., 2013; White et al., 2007). For example, in Guerra et al.’s (2000) study based on a survey of more than 85,000 U.S. high school students, African Americans were three times more likely than their European American counterparts to try illicit drugs before alcohol or cigarettes. Atypical sequences are also more common in individuals at high risk for substance use problems (Novins et al., 2001; Tarter et al., 2006). For instance, Mackesy-Amity et al. (1997) found that 22% of regular heroin and cocaine users used illicit drugs other than marijuana before both alcohol and marijuana.

Psychiatric correlates of atypical sequences of substance use initiation have only rarely been studied, and findings from the two studies—one a study of nicotine and marijuana use in 1,800 adolescents and young adults from high-risk families (Agrawal et al., 2011) and the second a population-based study of 13,000 adults in New Zealand (Wells and McGee, 2008)—have produced inconsistent findings. We are aware of only one study that examined

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order of initiation as a predictor of illicit drug dependence, and it showed no difference between typical and atypical sequences (Wells and McGee, 2008). Distinctions in the course of dependence (e.g., severity, duration) between typical and atypical sequence followers have yet to be explored.

The primary aim of this study was to estimate the proportion of cocaine-dependent users who follow atypical sequences of substance use initiation and characterize them with respect to demographic, psychiatric, and childhood risk factors. The sequence of initiation was examined in relation to both alcohol and marijuana. In addition to cocaine-dependent individuals who tried alcohol or marijuana first, we included those who never used alcohol and/or marijuana, a rarely studied subgroup of atypical drug users. The second aim of the study was to examine differences across sequences in indicators of the course of cocaine dependence, namely, severity and duration of cocaine dependence and likelihood of seeking treatment.

Method

Sample

Data were derived from cocaine-dependent individuals who participated in a multisite study conducted at Yale University, the University of Connecticut, the University of Pennsylvania, the University of South Carolina, and McLean Hospital. The sample for the multisite study was composed of alcohol-, cocaine-, or opioid-dependent individuals and unaffected controls recruited for case-control genetic studies of SUDs, as well as cocaine- or opioid-dependent probands and their relatives from family-based genetic studies. (See Sun et al., 2012, for details on sample and procedures.) The institutional review boards at all participating institutions approved the study.

The sample size for the current investigation was 6,333. The mean age was 40.4 ($SD = 9.0$) years. Forty-one percent of participants were female; 51.9% self-identified as African American, 39.7% as European American, and 8.4% as another race/ethnicity.

Assessment

Demographics, diagnostic criteria for lifetime DSM-IV psychiatric disorders, and history of childhood risk factors associated with SUDs (i.e., traumatic events and exposure to cocaine or heroin use in the home), along with a detailed history of substance use, were queried in in-person interviews using an electronic version of the Semi-structured Assessment for Drug Dependence and Alcoholism (SSADDA). A detailed description of the SSADDA, including administration and reliability, has been previously reported (Pierucci-Lagha et al., 2005, 2007).

Operationalization of variables

Substance use. Age at first use was asked of all participants who endorsed use of a given substance. Sequence of initiation was determined by comparing reported ages at first use of each substance. Participants were categorized with respect to both alcohol and marijuana as (a) never used alcohol/marijuana (*never used*), (b) first use of cocaine preceded first use of alcohol/marijuana (*used cocaine first*), or (c) first use of cocaine was at the same age or after first use of alcohol/marijuana (*same age/cocaine after*). Age at dependence onset was assessed by asking those who met dependence criteria the age at which they first experienced three or more of the endorsed symptoms within a 12-month period.

Severity of cocaine dependence was operationalized as the sum of abuse and dependence symptoms. Duration of dependence was calculated using reports of onset and offset ages. The distribution for duration was highly skewed, so we used quartiles to construct categorical variables: 4 or fewer, 5–10, 11–17, and at least 18 years. Treatment seeking was assessed with the question, “Have you ever been treated for a problem with cocaine?”

Other domains. Educational level was collapsed into a three-level variable: less than high school, high school, and greater than high school. Marital status was categorized as married, never married, and either separated, divorced, or widowed. Household income was dichotomized as \$10,000 or more versus less than \$10,000 (because of skewness). Psychiatric diagnoses were derived according to DSM-IV criteria. Exposures to childhood risk factors were assessed with yes/no questions.

Data analysis

Regression analyses were conducted in Stata (StataCorp LP, College Station, TX) using the Huber–White correction to adjust for non-independence of observations in family members. All analyses were adjusted for age. Analyses were conducted separately for alcohol and marijuana. First, the distributions across the three initiation sequences were calculated for alcohol and marijuana. Second, for both cocaine–alcohol and cocaine–marijuana initiation sequences, three multinomial regression models using (a) demographics, (b) SUDs and other psychiatric disorders, and (c) childhood risk factors were conducted to test for associations with sequences. The *same age/cocaine after* (typical sequence) group was the reference group. Third, the significant covariates from the domain-specific analyses were entered into final multinomial regression models. Fourth, severity, duration, and treatment-seeking outcomes were modeled, adjusting for covariates that were significant in the final multinomial regression models from Step 3. Ordinal regression analyses were used to analyze se-

verity (symptom count) and duration (categorical years dependence criteria met) outcomes. Logistic regression analyses were used to analyze treatment-seeking (dichotomous) outcomes. Duration models were adjusted for age at first use.

Results

Patterns of initiation of substance use

Information on alcohol use was available for 6,306 participants; information on marijuana use was available for 6,282. Just under 1% of participants (0.8%) reported never having a full drink of alcohol, 4.0% reported first cocaine use before first drink, and 95.2% reported age at first cocaine use as the same or older than age at first drink. In the case of marijuana, 5.2% reported never using, 3.4% reported using cocaine first, and 91.4% reported first use of cocaine at the same age or later than first use of marijuana.

Demographic, psychiatric, and childhood risk factors and sequences of initiation

Results of multinomial regression analyses testing for differences in the characteristics of participants across initiation sequences are shown in Table 1. Women were more likely than men to report never using alcohol or marijuana. Both abstention from alcohol and abstention from marijuana use were associated with lower likelihood of meeting nicotine dependence criteria. Race/ethnicity was not associated with abstaining from either alcohol or marijuana, but non-European Americans were more likely than European Americans to

report using cocaine before alcohol or marijuana. There was no overlap between covariates associated with initiation of cocaine before alcohol use and those associated with initiation of cocaine before marijuana use.

Both atypical sequences of cocaine and alcohol use (abstaining and using cocaine first) were associated with lower likelihood of meeting criteria for cannabis dependence but an elevated likelihood of meeting criteria for opioid dependence. The only commonality between the two atypical cocaine and marijuana sequences was the overrepresentation of women. Two covariates were associated exclusively with abstaining from marijuana: educational level above high school and alcohol dependence. Both were associated with a lower likelihood of abstaining from (i.e., greater likelihood of using) marijuana. The one significant finding specific to the cocaine before alcohol use sequence was lower rate of conduct disorder. The one specific to cocaine before marijuana use was death of a parent before age 6, which was associated with an increased likelihood of following this sequence.

Sequences of substance use initiation and course of dependence

Overall, the sequence of substance use initiation had little association with severity or duration of dependence or treatment seeking. After adjusting for significant covariates identified in multinomial regression models, the only significant finding was that individuals who had never used marijuana had lower symptom severity than those who initiated cocaine use at the same age as or after marijuana (odds ratio = 0.62, 95% confidence interval [0.47, 0.81]).

TABLE 1. Results of multinomial regression analyses examining potential differences in demographic factors and psychiatric disorders by sequence of first alcohol and marijuana use relative to first cocaine use among cocaine-dependent individuals^{a,b}

Variable	Alcohol		Marijuana	
	Never used alcohol RRR [95% CI]	Used cocaine first RRR [95% CI]	Never used marijuana RRR [95% CI]	Used cocaine first RRR [95% CI]
Female sex	2.80 [1.45, 5.38]*	1.22 [0.92, 1.62]	2.58 [1.96, 3.41]*	2.22 [1.57, 3.14]*
Ethnicity ^c				
African American	1.81 [0.93, 3.53]	2.07 [1.45, 2.95]*	0.96 [0.70, 1.30]	1.65 [1.07, 2.55]*
Other non-European American	1.43 [0.45, 4.55]	1.97 [1.18, 3.28]*	1.18 [0.72, 1.94]	2.45 [1.41, 4.25]*
Education level				
Below high school	N.S.	N.S.	0.98 [0.72, 1.35]	1.33 [0.88, 2.03]
Greater than high school	N.S.	N.S.	0.58 [0.40, 0.85]*	1.00 [0.61, 1.63]
Alcohol dependence	—	—	0.64 [0.48, 0.87]*	0.80 [0.54, 1.18]
Conduct disorder	0.58 [0.21, 1.58]	0.60 [0.39, 0.92]*	N.S.	N.S.
Cannabis dependence	0.26 [0.11, 0.60]*	0.58 [0.43, 0.80]*	—	—
Nicotine dependence	0.48 [0.25, 0.91]*	0.82 [0.60, 1.11]	0.57 [0.42, 0.76]*	0.91 [0.62, 1.36]
Opioid dependence	4.51 [2.43, 8.35]*	1.76 [1.29, 2.41]*	N.S.	N.S.
Death of a parent before age 6	N.S.	N.S.	1.12 [0.63, 2.00]	2.43 [1.38, 4.31]*
Witnessed violent crime before age 14	N.S.	N.S.	0.59 [0.41, 0.87]	0.91 [0.61, 1.35]

Notes: RRR = relative risk ratio; CI = confidence interval; N.S. = non-significant in univariate model, not entered into multivariate model. ^aAdjusted for age; ^bcomparison group = group that first used cocaine at the same age or after first use of alcohol/marijuana; ^ccomparison group = European Americans.

* $p < .05$.

Discussion

Our investigation of the sequence of substance use initiation in dependent cocaine users extends the literature in several ways. First, as one of the first studies examining sequence of initiation to include illicit drug users who abstained from alcohol and/or marijuana, the results provide a rare view into the characteristics of this subgroup of atypical drug users. Second, by focusing exclusively on individuals with a lifetime diagnosis of cocaine dependence, we indirectly addressed the question of whether the ordering of initiation of use is relevant to cocaine-related problems rather than simply risk for experimentation. Third, the indicators of dependence course that we examined (severity, duration, and treatment seeking) have not been investigated in prior studies of the sequence of substance use initiation.

Results revealed that, among cocaine-dependent individuals, it was much more common to abstain from marijuana (5.2%) than alcohol use (0.8%). However, the proportion of the sample reporting first use of cocaine before alcohol was about the same as the proportion reporting first use of cocaine before marijuana, approximately 4%. Despite the relatively small sizes of these groups, we were able to distinguish between typical and atypical sequences of cocaine use initiation with respect to demographics and psychiatric correlates.

Correlates of substance use initiation sequences

Several distinguishing characteristics were observed in individuals following an atypical sequence of substance use initiation, but none was present across substances for both abstainers and those who used cocaine first. Women were more likely to abstain from alcohol or marijuana use but not to use cocaine first, whereas non-European Americans were more likely than European Americans to use cocaine before alcohol or marijuana but not to abstain from use. With the exception of conduct disorder, which was associated with using cocaine before alcohol, psychiatric correlates of atypical sequences of initiation were limited to other SUDs. The one sequence of initiation not associated with any psychiatric disorders, cocaine before marijuana use, was also the only one related to any childhood risk factor (death of a parent before age 6). Overall, the overlap—both across and within substances—was modest, suggesting that these patterns of use represent different subgroups of dependent cocaine users.

The literature on characteristics distinguishing typical from atypical sequence followers is largely limited to demographics. However, two studies also included psychiatric disorders in their examination of the sequence of substance use initiation. Agrawal et al. (2011) found no association between the ordering of nicotine and marijuana use and a range of psychiatric disorders, including alcohol, nicotine, and cannabis use disorders. In Wells and McGee's (2008)

investigation, which was more similar to ours in its focus on drugs other than marijuana (including cocaine), the only psychiatric correlate of risk for use of other illicit drugs before marijuana was early-onset internalizing disorders. However, they did not include other SUDs in their analyses. Thus, our finding of lower rates of alcohol, nicotine, and cannabis dependence and elevated rates of opioid dependence with various atypical sequences (and one externalizing disorder correlated with one atypical sequence) is not consistent with either of the studies in this area.

We found that cocaine-dependent women were more likely than their male counterparts to abstain from alcohol or marijuana use but were no different with respect to trying cocaine first. The two known investigations to examine potential sex differences in deviation from the typical sequence of substance use initiation did not include individuals who abstained from alcohol or marijuana, so there are no comparable studies for our abstainer group findings. Among these two, one (Wells and McGee, 2008) produced results consistent with the absence of sex differences in rates of atypical ordering of first use in our study, but the other reported lower rates of atypical sequences in women (Degenhardt et al., 2009). By contrast, our finding that non-European Americans were significantly more likely than European Americans to use cocaine before alcohol or marijuana is consistent with numerous studies reporting greater deviation from the typical sequence of substance use initiation among African Americans than European Americans (Ellickson et al., 1992; Guerra et al., 2000; Sartor et al., 2013; White et al., 2007).

Sequences of substance use initiation and course of dependence

We found that individuals who used cocaine before alcohol or marijuana did not report a greater number of symptoms or longer duration of cocaine dependence nor were they more likely than the other groups to seek treatment. This may be due in part to the inclusion of covariates that distinguish sequences of initiation in this series of analyses. Several of those covariates, including other SUDs, are also related to severity of dependence and likelihood of seeking treatment (Ford et al., 2009).

Limitations

Certain limitations should be considered in interpreting our findings. First, retrospective reports may produce a retrospective reporting bias, which is relevant to the present study if it varies systematically by race/ethnicity or sex. Second, results may not generalize to non-dependent cocaine users. Third, our sample was ascertained based on SUD status and thus represents individuals typically seen in clinical settings, who differ in certain ways (e.g., severity of dependence) from those in the general population (Bucholz et al., 1994).

Conclusions and future directions

Although only a minority of dependent cocaine users deviate from the typical sequence of substance use initiation, these subgroups have certain distinguishing characteristics that are relevant to the development of prevention efforts. The profiles of these atypical groups underscore the importance of recognizing that the use of “hard” drugs can occur before or even in the absence of any alcohol or marijuana use. They also highlight the need to diversify prevention efforts to better meet the needs of young women and members of racial/ethnic minority groups, who are more likely than European American men to deviate from the typical sequence of initiation.

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