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Probability and predictors of transition from first use to dependence on nicotine, alcohol, cannabis, and cocaine: Results of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC)*

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Abstract

Background—This study aims to estimate general and racial-ethnic specific cumulative probability of developing dependence among nicotine, alcohol, cannabis or cocaine users, and to identify predictors of transition to substance dependence.

Methods—Analyses were done for the subsample of lifetime nicotine (n=15,918), alcohol (n=28,907), cannabis (n=7,389) or cocaine (n=2,259) users who participated in the first and second wave of the National Epidemiological Survey on Alcohol and Related Conditions (NESARC). Discrete-time survival analyses were implemented to estimate the cumulative probability of transitioning from use to dependence and to identify predictors of transition to dependence.

Results—The cumulative probability estimate of transition to dependence was 67.5% for nicotine users, 22.7% for alcohol users, 20.9% for cocaine users, and 8.9% for cannabis users. Half of the cases of dependence on nicotine, alcohol, cannabis and cocaine were observed approximately 27, 13, 5 and 4 years after use onset, respectively. Significant racial-ethnic differences were observed in the probability of transition to dependence across the four substances. Several predictors of dependence were common across the four substances assessed.

*Supplementary data tables are available with the online version of this article. See Appendix A.

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Appendix A. Supplementary data tables 5 and 6 associated with this article can be found in the online version of this article at doi: 10.1016/j.drugalcdep.xxxx.xx.xxx.

Conclusions—Transition from use to dependence was highest for nicotine users, followed by cocaine, alcohol and cannabis users. Transition to cannabis or cocaine dependence occurred faster than transition to nicotine or alcohol dependence. The existence of common predictors of transition dependence across substances suggests that shared mechanisms are involved. The increased risk of transition to dependence among individuals from minorities or those with psychiatric or dependence comorbidity highlights the importance of promoting outreach and treatment of these populations.

Keywords

nicotine; alcohol; cannabis; cocaine; dependence; racial-ethnic groups; discrete-time time survival analyses

1. Introduction

Although only a small proportion of individuals who use addictive substances develop dependence (United Nations Office on Drugs and Crime., 2007), substance dependence represents a tremendous burden to the individual and to society (World Health Organization., 2002). Estimating the risk and predictors of transition from substance use to dependence can provide information about the etiology and course of addiction, guide clinicians in identifying patients at higher risk of becoming dependent, and assist in the organization of primary and secondary prevention services.

Previous epidemiological studies have found that between one-third to one-half of daily nicotine smokers develop nicotine dependence at some point in their lives (Anthony et al., 1994; Breslau et al., 2001; Dierker et al., 2008; Kandel et al., 1997) and that, within a decade of alcohol, cannabis and cocaine use, 12%-13% develop alcohol dependence, 8% cannabis dependence and 15%-16% cocaine dependence (Wagner and Anthony, 2002a). Several risk factors for the transition from use to dependence have been identified, including being young, male, Black or Native-American, poor, with low levels of educational attained, urban residence, early substance use onset, use of another psychoactive substance, and co-occurrence of a psychiatric disorder (Behrendt et al., 2009; Breslau et al., 2001; Chen et al., 2005; Dawson et al., 2008; Grant and Dawson, 1997, 1998; Kandel et al., 1997; O'Brien and Anthony, 2005; Reardon and Buka, 2002; Wagner and Anthony, 2002a, 2007; Warner et al., 1995).

Despite the significant contributions from previous studies, important questions remain regarding the factors influencing transition from substance use to dependence. For example, most studies have examined all substances together (Kessler et al., 2001; Merikangas et al., 1998) or focused on a single substance (Breslau et al., 2001; Chen et al., 2005; O'Brien and Anthony, 2005), precluding formal examination of similarities and differences of predictors across substances. Psychiatric comorbidity, a consistent predictor of transition in many studies (Kessler et al., 1997; Merikangas et al., 1998) has been often examined as a single category (Merikangas et al., 1998) or analyzed as invariant over time (Breslau, 1995; Sintov et al., 2009). Few studies have examined racial-ethnic differences in the rates and determinants of transitioning from use to dependence (Grant, 1996; Grant et al., 2004b; Kandel et al., 1997; Ridenour et al., 2005).

To fill these gaps in knowledge, we sought to estimate the risk and identify the predictors of transition from substance use to dependence in a large, nationally representative sample of U.S. adults. The specific goals of this study were: 1) to estimate the general and racial-ethnic specific cumulative probability of developing dependence among nicotine, alcohol, cannabis and cocaine users, and, 2) to assess the association between several socio-demographic

characteristics, psychiatric comorbidity and drug-use related variables and the risk of transition to dependence among users of these substances.

2. Methods

2.1 Sample and procedures

The 2004-2005 Wave 2 NESARC (Grant et al., 2007b) is the second wave of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC)(Grant et al., 2003a). The target population was the civilian non-institutionalized population 18 years and older residing in households and group quarters (GQ) (e.g., college quarters, group homes, boarding houses, and non-transient hotels). Blacks, Hispanics, and adults ages 18-24 were oversampled.

Of the 43,093 respondents interviewed at Wave 1, 34,653 respondents were re-interviewed at Wave 2. Census-defined eligible for Wave 2 re-interviews included those not deceased (n=1403), deported, mentally or physically impaired (n=781) or on active military duty (n=950). Sample weights were developed to additionally adjust for Wave 2 non-response. Specifically, weights adjusted for the probabilities of selection of a sample housing unit or housing unit equivalent from the GQ, nonresponse at the household and person levels, the selection of one person per household, and oversampling of young adults. Once weighted, data were adjusted to be representative of the US population for region, age, sex, race, and ethnicity. After adjustment, comparisons between Wave 2 respondents and the target population (comprising Wave 2 respondents and eligible non-respondents) indicated that there were no significant differences in terms of a number of baseline (Wave 1) socio-demographic measures or the presence of any lifetime substance, mood, anxiety or personality disorder (PD) (Grant et al., 2007a). This study examines data of the sub-sample of lifetime nicotine (n=15,918), alcohol (n=28,907), cannabis (n=7,389) or cocaine (n=2,259) users.

2.2 Data collection

Data was collected using the National Institute on Alcohol Abuse and Alcoholism Alcohol - Alcohol Use Disorder and Associated Disabilities Interview Schedule-DSM-IV (AUDADIS-IV), (Grant et al., 2001a), version Wave 2 (Grant et al., 2004a). The AUDADIS-IV is a structured diagnostic interview, developed to advance measurement of substance use and mental disorders in large-scale surveys (Grant et al., 2008; Grant et al., 2004e). Computer algorithms produced DSM-IV diagnoses based on AUDADIS-IV data collected at Wave 1 (prevalence cases) and Wave 2 (incident cases between Wave 1 and Wave 2).

2.3 Measures

2.3.1 Substance use and dependence—Extensive AUDADIS-IV questions covered DSM-IV criteria for alcohol and drug-specific abuse and dependence for 10 classes of substances (sedatives, tranquilizers, painkillers, stimulants, cannabis, cocaine or crack, hallucinogens, Inhalants/solvents, Heroin, alcohol and nicotine). Substance use and age of substance use onset was determined by asking respondents about the age at which they first "smoked a first full cigarette" (nicotine use), "had at least 1 drink of any kind of alcohol (not counting small tastes or sips)" (alcohol use), used cannabis (cannabis use), or used cocaine or crack (cocaine use). Dependence on these substances was assessed separately via extensive items covering the DSM-IV criteria (American Psychiatric Association, 1994), which require 3 or more of 7 criteria within a 12-month period. Drug-specific dependence criteria were aggregated to yield diagnoses of drug dependence for each substance. The presence of symptoms for time periods whose duration was greater than 1 year, was assessed

by asking the study participants the occurrence of those symptoms “on and off for a few months or longer”, “most days for at least a month,” or “within the same 1-year period”. A previous diagnosis of a substance use disorder (SUDs, abuse or dependence) to any of the 10 substances assessed in the AUDADIS IV was also included as a covariate.

The good to excellent (κ=0.54-0.91) test-retest reliability and validity of AUDADIS-IV SUD diagnoses is well documented in clinical and general population samples (Grant et al., 2003b; Hasin et al., 1997; Hasin et al., 2003; Ruan et al., 2008).

2.3.2 Psychiatric disorders—Mood disorders included DSM-IV primary major depressive disorder, dysthymia, bipolar I, and bipolar II. Anxiety disorders included DSM-IV primary panic disorder (with and without agoraphobia), social anxiety disorder, specific phobias, generalized anxiety disorder and post-traumatic stress disorder (PTSD). AUDADIS-IV methods to diagnose these disorders are described in detail elsewhere (Grant et al., 2005a; Grant et al., 2005b; Grant et al., 2005c; Hasin et al., 2005a; Stinson et al., 2007). Psychotic and conduct disorders were assessed in the Wave 1 of the NESARC and attention-deficit/hyperactivity disorder (ADHD) and PTSD were only assessed in the Wave 2 of the NESARC. Consistent with DSM-IV, “primary” AUDADIS-IV diagnoses excluded disorders that are substance-induced or due to general medical conditions.

Avoidant, dependent, obsessive-compulsive, paranoid, schizoid, histrionic, and antisocial and PDs were assessed on a lifetime basis at Wave 1 and described in detail elsewhere (Grant et al., 2004c). Borderline, schizotypal, and narcissistic PDs were measured at Wave 2. Personality disorder diagnosis required long-term patterns of social and occupational impairment (Grant et al., 2004d).

Test-retest reliabilities for AUDADIS-IV mood, anxiety and PD diagnoses in the general population and clinical settings were fair to good (κ=0.40-0.77) (Canino et al., 1999; Grant et al., 2003b; Ruan et al., 2008). Convergent validity was good to excellent for all affective, anxiety, and PD diagnoses (Grant et al., 2004c; Hasin et al., 2005b), and selected diagnoses showed good agreement (κ=0.64-0.68) with psychiatrist reappraisals (Canino et al., 1999).

2.3.3 Demographic and other substance use-related variables Socio-demographics—Self-reported race/ethnicity was recoded into 5 groups: Whites, Blacks, Hispanics, Native Hawaiians or other Pacific Islanders (NH/PI) and American Indians or Alaskan Natives (AI/AN). Other socio-demographic factors included gender, age, urbanicity (urban vs. rural), nativity (US-born vs. foreign-born), level of education, individual and family income, marital status, and employment status. Early substance use onset (before age 14) and family history of SUDs (any alcohol or drug use disorder among first degree relatives) were also included as substance use-related covariates.

2.4 Analyses

Weighted frequencies and their respective 95% confidence intervals (95% CI) were computed to characterize the sample. Estimated projections of the cumulative probability of transitioning from use to dependence within the first year of substance use onset, the first decade after substance use onset, and lifetime in the general population and by racial-ethnic group were obtained by the standard actuarial method (Machin et al., 2006) as implemented in PROC LIFETEST in SAS (version 9.1.3), (SAS Institute, Cary, N.C.). The log-rank test was used to determine whether survival curves differed statistically across substances and across racial-ethnic groups for each substance.

Univariate and multivariable discrete-time survival analyses (with person-year as the unit of analysis) (Jenkins, 1995) were implemented using SUDAAN version 9.1, (Research

Triangle Institute, Research Triangle Park). The models aimed at assessing the association between socio-demographic, psychiatric comorbidity and substance use-related covariates and the hazards of transition to substance dependence. The person-year variable was defined as the number of years from substance use onset to age of dependence onset or age at Wave 2 interview (for censored cases). Education, marital status, and presence of DSM-IV mood, anxiety, and SUDs other than the one under examination were included as time-dependent covariates. Stepwise model selection procedures were used to identify independent correlates based on likelihood-ratio test. Taylor series linearization methods implemented in SUDAAN were used to estimate standard errors and significance, and to accommodate for the complex survey design. All estimates were obtained using Wave 2 weights.

3. Results

3.1 Sociodemographic characteristics

Socio-demographic characteristics of the study populations are presented in table 1. Rates of nicotine, alcohol, cannabis and alcohol use were higher among males, Whites and AI/AN and US-born individuals. While rates of nicotine and cannabis use were higher among individuals in the youngest age group (18 to 29 years old), rates of alcohol and cocaine use were higher among individuals 30 to 44 years old. Respondents less educated and with an individual income lower than $35,000 reported higher rates of nicotine use. Respondents who completed at least some college education or had an individual income equal or higher than $70,000 reported higher rates of alcohol, cannabis or cocaine use. While divorced/ separated individuals reported higher rates of nicotine, alcohol and cocaine use, never married individuals reported higher rates of cannabis use.

3.2 Psychiatric and Substance Use Comorbid Disorders

Psychiatric and substance use comorbid disorders as well as other substance use-related characteristics of the study populations are presented in table 2. Rates of nicotine, alcohol, cannabis and cocaine use were higher among individuals reporting any lifetime psychiatric disorder, mood disorder, anxiety disorder, conduct disorder, personality disorder or ADHD. Individuals with a family history of a SUD or having a diagnosis of a SUD reported higher rates of use of all the substances assessed. Characteristics of individuals who developed dependence on the four substances are presented in supplementary tables available with the online version of this article (Appendix A).

3.3 Probability of transitioning to substance dependence among substance users

After the first year of substance use onset the probability of transition to dependence was almost 2.0% for nicotine, alcohol and cannabis users and 7.1% for cocaine users. The probability estimates of transition to dependence a decade after use onset was 15.6% among nicotine users, 14.8% among cocaine users, 11.0% among alcohol users, and 5.9% among cannabis users. Lifetime cumulative probability estimates indicated that 67.5% of nicotine users, 22.7% of alcohol users, 20.9% of cocaine users, and 8.9% of cannabis users would become dependent on those substances at some time in their life. Half of the cases of nicotine, alcohol, cannabis and cocaine dependence were observed approximately 27, 13, 5 and 4 years after use onset, respectively (Figure 1).

3.3.1 Racial differences in transition to nicotine dependence—Among nicotine users, 64.1% of Whites, 70.7% of Blacks, 64.7% of Hispanics, 64.5% of NH/PI, and 85.1% of AI/AN transitioned to dependence at some time in their life (log rank test= 41.53, $p<0.01$). Half of the cases of nicotine dependence among Whites, Blacks, Hispanics, NH/PI and AI/AN developed approximately 23, 30, 26, 18 and 24 years after use onset, respectively (Figure 2).

3.3.2 Racial differences in transition to alcohol dependence—Among alcohol users, 22.6% of Whites, 21.4% of Blacks, 26.7% of Hispanics, 16.9% of NH/PI and 29.0% of AI/AN transitioned to dependence at some time in their life (log rank test= 47.16, $p<0.01$). Half of the cases of alcohol dependence among Whites, NH/PI and AI/AN developed approximately 8 years after the first use, whereas among Blacks and Hispanics alcohol dependence developed approximately 16 years after the first use (Figure 2).

3.3.3 Racial differences in transition to cannabis dependence—Among cannabis users, 8.2% of Whites, 9.7% of Blacks, 10.0% of Hispanics, 15.9% of NH/PI, and 14.8% of AI/AN (log rank test= 17.57, $p<0.01$) transitioned to dependence at some time in their life. Half of the cases of cannabis dependence among Whites, Blacks, Hispanics, and AI/AN developed approximately 5 years after the first use. NH/PI developed cannabis dependence approximately 10 years after the first use (Figure 2).

3.3.4 Racial differences in transition to cocaine dependence—Among cocaine users, 16.8% of Whites, 35.9% of Blacks, 20.5% of Hispanics, 20.3% of NH/PI, and 22.5% of AI/AN transitioned to dependence at some time in their life (log rank test= 30.40, $p<0.01$). Half of the cases of cocaine dependence among Whites, Blacks, Hispanics, NH/PI and AI/AN developed approximately 2, 3, 4, 5 and 4 years, after the first use, respectively (Figure 2).

3.4 Predictors of transition from substance use to dependence

In univariate and multivariable discrete-time survival models several socio-demographic, psychopathological and substance use-related variables predicted transition from substance use to dependence for most of the substances assessed (Tables 3 and 4).

3.4.1 Socio-demographic predictors—According to the adjusted models (Table 4), males were less likely than females to transition from nicotine use to dependence, and more likely to transition from alcohol and cannabis use to dependence. Individuals younger than 45 years old were significantly more likely to transition to dependence for any of the substances assessed than those older than 45 years old. Compared to White nicotine users, Hispanic nicotine were less likely to transition to dependence and NH/PI and AI/AN nicotine users were more likely to transition to dependence. Compared to White alcohol users, Black alcohol users were less likely to transition to dependence. Compared to White cannabis users, AI/AN cannabis users were more likely to transition to dependence. Compared to White cocaine users, Black cocaine users were notably more likely to transit to dependence.

US-born Individuals were more likely than foreign-born individuals to report transition from nicotine and alcohol use to dependence. Compared to nicotine or alcohol users married or living with someone, those never married were more likely to report transition to dependence. Compared to cocaine users married or living with someone, those widowed, divorced or separated were more likely to report transition to dependence. Nicotine and alcohol users who reported ever having been employed showed a lower likelihood of transitioning to dependence. Neither education, nor income predicted transition to dependence.

3.4.2 Psychopathological and substance use-related predictors—A history of any mental disorder strongly predicted the development of substance dependence. For instance, nicotine, alcohol, cannabis or cocaine users diagnosed with a mood disorder or a PD were more likely to become dependent on those substances than individuals who did not report having had any of these disorders. As presented in table 4, controlling for the effect of

other covariates did not appreciably modified the results. Nicotine, alcohol or cannabis users diagnosed with an anxiety disorder showed an increased risk of becoming dependent on these substances in the adjusted models. A lifetime diagnosis of a psychotic disorder increased the risk of developing nicotine dependence among nicotine users in the adjusted model.

Having a history of SUD predicted a further development of an additional SUD (Table 4). Individuals diagnosed with nicotine dependence were more likely to develop alcohol dependence among alcohol users, and cannabis dependence among cannabis users. Nicotine, cannabis and cocaine users diagnosed with alcohol dependence showed a higher risk of developing dependence on these substances. Nicotine, alcohol and cocaine users diagnosed with cannabis dependence showed increased hazards of developing dependence on these substances. Nicotine, alcohol and cannabis users diagnosed with cocaine dependence were more likely to develop dependence on these substances.

Family history of SUD increased the risk of transition from nicotine or alcohol use to dependence (table 4). Individuals who used nicotine, before age 14 exhibited higher hazards of becoming nicotine dependent than individuals who started to use it after that age. Individuals who used cannabis or cocaine before age 14 were less likely to transit to dependence on these substances (table 4).

4. Discussion

In a large, nationally representative sample of US adults, the cumulative probability of transition to dependence was highest for nicotine users, followed by cocaine users, alcohol users and, lastly, cannabis users. The transition to cannabis or cocaine dependence occurred faster than the transition to nicotine or alcohol dependence. Furthermore, there were important variations in the probability of becoming dependent across the different racial-ethnic groups. Most predictors of transition were common across substances.

Consistent with previous estimates from the National Comorbidity Survey (Wagner and Anthony, 2002a), the cumulative probability of transition from use to dependence a decade after use onset was 14.8% among cocaine users, 11.0% among alcohol users, and 5.9% among cannabis users. This probability was 15.6% among nicotine users. Furthermore, lifetime cumulative probability estimates indicated that 67.5% of nicotine users, 22.7% of alcohol users, 20.9% of cocaine users, and 8.9% of cannabis users would become dependent at some time in their life. Pharmacokinetic, environmental and physiological factors may contribute to explain the higher rates of transition from nicotine use to dependence compared to transition from use to dependence of other substances. For instance, the rate of absorption in the extensive surface area of alveoli attained from smoking nicotine (Henningfield and Keenan, 1993; Samaha and Robinson, 2005) is far greater than the rate of absorption of alcohol or cocaine in the nasal and gastro-intestinal mucosae (Fattinger et al., 2000; Norberg et al., 2003). The higher social acceptability of nicotine use compared to other substances also increases the exposure to environmental, situational and sensorial cues that evoke craving for its consumption (Benowitz, 2008; Hatsukami et al., 2008). Furthermore, nicotine use does not produce the notorious disruptive behavioral changes that alcohol, cannabis and cocaine use often engender (Benowitz, 2008; Hatsukami et al., 2008).

Variations in the effect of molecular mechanisms underlying addiction-associated neuroadaptations in several regions of the brain (Adinoff, 2004; Benowitz, 2008; Lupica et al., 2004; Moussas et al., 2009; Nestler, 2005), may also contribute to explain differences in the probability of transition across substances (Renthal and Nestler, 2008). Chronic drug exposure results in the accumulation of ΔFosB, which increases the sensitivity to the

reinforcing effects of drugs (Perrotti et al., 2008; Renthal and Nestler, 2008; Wallace et al., 2008). Chronic exposure to Δ^9-tetrahydrocannabinol, the active ingredient in cannabis, produces a less dramatic effects on ΔFosB induction in the nucleus accumbens shell and dorsal striatum than the effect observed after chronic exposure to cocaine and alcohol (Perrotti et al., 2008).

Consistent with previous studies (Anthony et al., 1994; Behrendt et al., 2009; Breslau et al., 2001; Chen et al., 2005; O'Brien and Anthony, 2005; Ridenour et al., 2003; Ridenour et al., 2005; Wagner and Anthony, 2002a, 2007), the lag period from substance use onset to dependence was greater for nicotine and alcohol than for cannabis or cocaine. Differences in the speed of transition from use to dependence may be related to addictive liability and pharmacokinetic properties of the substances (Koob and Volkow, 2009; Lupica et al., 2004; Nestler, 2005; Ridenour et al., 2005), as well as their availability, legality and social acceptability (Ridenour et al., 2005). Confirming prior findings (Agrawal et al., 2008; Drgon et al., 2006; Kandel, 2002; Stinson et al., 2005), use of and dependence on other substance increased the risk of transition to dependence. In our sample, one third of alcohol users and half of nicotine users had an additional SUD, compared to more than 80% of cannabis users and 90% of cocaine users. The accelerated speed of transition from cannabis or cocaine use to dependence given a previous history of a SUD may be mediated by conditioned learning processes, faster neuroadaptations (Leri et al., 2003; Schlaepfer et al., 2008) and drug interactions leading to slower biotransformation, decreases in adverse drug effects and overall enhanced drug effects (Bradberry et al., 1999; Kapusta et al., 2007; Leri et al., 2003; Mayer, 1984). Individuals dependent on more than one substance appear to have higher genetic liability and alleles of several genes have been associated with polysubstance abuse (Agrawal et al., 2008; Drgon et al., 2006; Schlaepfer et al., 2008). Yet, the simultaneous use of multiple drugs is not entirely explained by genetic factors, with environmental influences playing an important role (Agrawal et al., 2004). Exposure to areas with high levels of social disadvantage facilitates access not only to one but to several drugs, (Storr et al., 2004; Wagner and Anthony, 2002b), which may normalize polysubstance use behaviors. The rapid transition from cannabis and cocaine use to dependence emphasizes the need for aggressive preventive interventions among users of these substances.

Blacks, NH/PI and AI/AN had the highest rates of transition from use to dependence. Acculturative stress and racial/ethnic discrimination may help explain the increased risk of transition from use to dependence among these minority groups (Caraballo et al., 2008; Chae et al., 2008; Kim et al., 2007). Experiencing a stressful event, like discrimination, may promote the utilization of maladaptive coping mechanisms, such as substance use (Gibbons et al., 2004; Whitbeck et al., 2001), or produce enduring neurochemical changes leading to develop a SUD (Koob, 2009). Low social capital, common among AI/AN and Blacks may further increase the risk of transition (Beauvais et al., 2004; Fothergill et al., 2009; U.S. Department of Health and Human Services, 1998). Furthermore, several biological mechanisms and genetic factors may also contribute to explain racial-ethnic variations in the risk of transition to SUD. Genetic influences have accounted for a significant amount of the variance in the development of SUD among AI/AN (Ehlers et al., 2009; Wilhelmsen and Ehlers, 2005). Genetic factors involved in nicotine and cotinine metabolism may contribute to variations in the amount of daily tobacco consumption in several racial-ethnic groups (Benowitz et al., 2009). For instance, Hawaiian (Derby et al., 2008) and Canadian Native-Americans (Hukkanen et al., 2005; Schoedel et al., 2004) smokers exhibit increased activity of the cytochrome P450 2A6 (CYP2A6), the primary enzyme that inactivates nicotine to cotinine. This increased activity may lead them to increased daily tobacco consumption and vulnerability to develop nicotine dependence.

Psychiatric comorbidity predicted transition to dependence, as previously reported (Breslau et al., 2004; Glantz et al., 2008; Kessler, 2004; Kessler et al., 1996; Zimmermann et al., 2003). The co-occurrence of mental and SUD may be due to self-medication practices or the existence of common liability factors (Leonard et al., 2007; Neale and Kendler, 1995; van Os et al., 2002). Family, twin and genome-wide studies suggest that genetic factors are largely responsible for the pattern of comorbidity of common psychiatric and substance use disorders (Burmeister et al., 2008; Kendler et al., 2003; Li and Burmeister, 2009). For example, individuals with a lifetime history of a psychotic disorder had an increased risk of transition to nicotine dependence. Recent findings have linked mutations in the neurexin 1 gene, a cell adhesion-related gene, to an increased risk for nicotine dependence or schizophrenia (Leonard et al., 2007; Nussbaum et al., 2008; Rujescu et al., 2009). Heightened impulsivity and disturbances in reward motivation are also common risk factors across several psychiatric disorders that can explain their co-occurrence (Agrawal et al., 2004; Chambers and Potenza, 2003). Prevention and treatment of mental disorders may decrease the risk of transition from substance use to dependence.

Results of the unadjusted models indicate that individuals with an early use onset had an increased risk of transition to dependence, which is consistent with the result of previous epidemiological studies (Behrendt et al., 2009; Dawson et al., 2008; Grant et al., 2001b). However, after controlling for the effect of socio-economic, psychiatric comorbidity and drug-use covariates, the direction of this association changed for cannabis and cocaine, indicating that the higher risk of developing dependence on these substances among those who reported an early use onset was mostly explained by those factors. Therefore, the risk of transitioning to dependence may not be a consequence of early substance use onset per se, but rather of the existence of a concomitant psychiatric and SUD that increase the risk of developing a SUD (Behrendt et al., 2009; Degenhardt et al., 2009; Wittchen et al., 2007). The higher risk of transitioning to cannabis and cocaine dependence among those individuals with later use onset, may also be due to the emergence of more intense patterns of use, greater availability and affordability of these drugs in late adolescence and higher social acceptability (Bachman et al., 1998; Behrendt et al., 2009; Kandel, 2002). Consistent with previous findings (Behrendt et al., 2009), the positive association between early onset of nicotine use and transition to dependence remained significant after controlling for other covariates.

The present findings should be interpreted in light of common limitations in most large-scale surveys. First, information on substance use and SUD was based on self-report and not confirmed by objective methods. Second, diagnoses may be subject to recall bias (the longer the time interval between the event and assessment, the higher the probability of incorrect recalls) and to cognitive impairment associated with the use of drugs (Grant et al., 2003c; Hasin and Liu, 2003). Third, in some cases, substance use may have been intermittent, rather than continuous, which would produce inexact estimates of the time elapsed from use onset to dependence. Fourth, the NESARC excludes institutionalized populations, who have an increased probability of having a diagnosis of substance dependence (McCutcheon et al., 2009). Fifth, factors that may help explain the racial-ethnic differences, such as income could not be included in the models as time-dependent covariates since the NESARC, as most large scale surveys, does not include information on changes in income overtime.

In summary, the rate of transition from use to dependence is higher for nicotine user than for alcohol, cannabis or cocaine users. Individuals from some ethnic minority groups and those with a history of psychiatric and substance dependence comorbidity showed an increased risk of transitioning from use to dependence. Several predictors of dependence were common across the substances assessed, suggesting the existence of shared mechanisms. Promoting outreach and treatment of individuals from minority population groups or those

with a primary mental disorder may constitute an important strategy to prevent transition to substance dependence.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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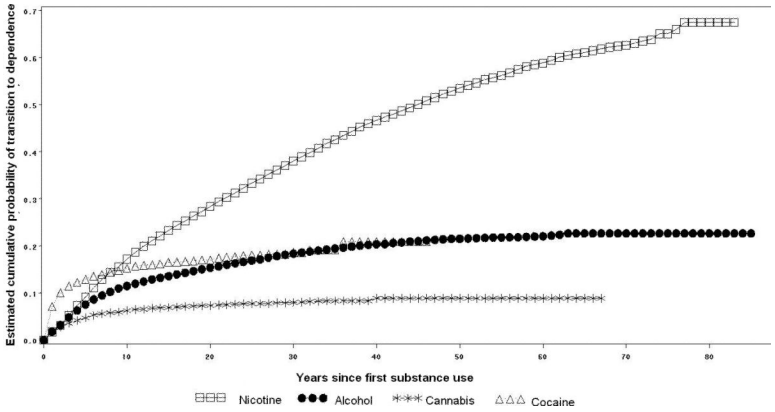

Figure 1.
Cumulative probability of transitioning to dependence on nicotine, alcohol, cannabis and cocaine among users of these substances

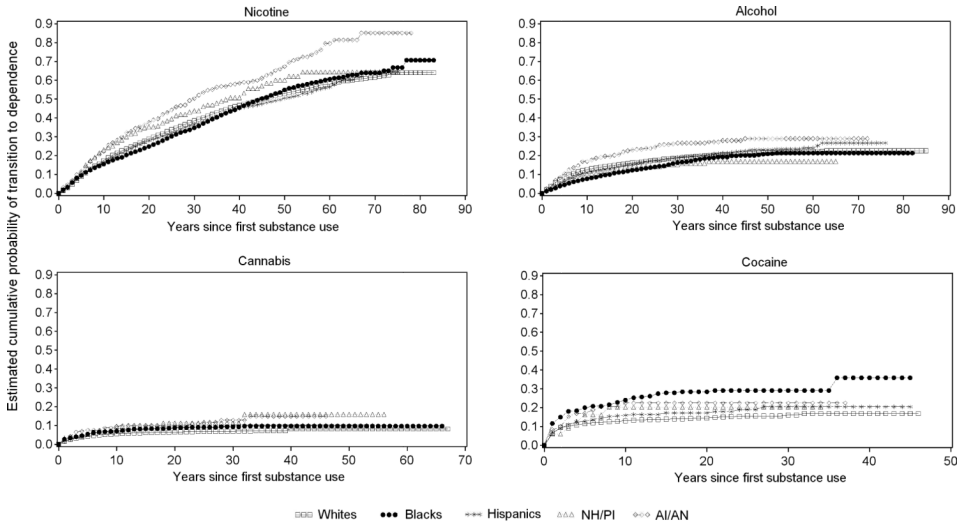

Figure 2.
Cumulative probability of transitioning to dependence among nicotine, alcohol, cannabis and cocaine users by racial-ethnic group

Table 1

Socio-demographic characteristics of individuals with lifetime history of nicotine, alcohol, cannabis and cocaine use (weighted percentages).

Characteristic	Nicotine Use N=15,918		Alcohol Use N=28,907		Cannabis Use N=7,389		Cocaine Use N=2,259	
	N	%	N	%	N	%	N	%
Gender								
Male	8301	57.2	13197	92.5	3919	26.9	1306	9.0
Female	7752	38.8	15963	81.6	3490	17.4	957	4.8
Age group								
18-29	1992	40.7	4281	88.1	1539	31.3	328	6.7
30-44	4239	40.1	9358	89.7	2998	28.3	1005	9.5
≥45	9822	51.8	15521	83.8	2872	15.0	930	4.87
Race/ethnicity								
Whites	10581	52.8	17805	90.3	4897	24.3	1512	7.5
Blacks	2703	41.5	5169	80.8	1179	17.9	275	4.2
Hispanics	2155	34.1	5033	81.3	1027	16.2	383	6.0
NH/PI	268	27.9	660	70.4	118	12.2	33	3.4
AI/AN	346	60.3	493	86.5	188	32.6	60	10.4
Urbanicity								
Rural	2587	46.5	4679	85.6	1187	21.2	391	7.0
Urban	13466	46.7	24481	86.3	6222	21.4	1872	6.5
Nativity								
US-Born	14465	49.7	25317	88.5	6990	23.9	2134	7.3
Foreign-born	1588	29.8	3843	74.0	419	7.8	129	2.4
Education								
< High school	2757	50.7	3900	73.7	719	13.1	246	4.5
High school	3990	49.1	6672	83.6	1410	17.2	451	5.5
≥ College	9306	44.6	18588	90.5	5280	25.2	1566	7.5
Individual income								
$0-$19,999	6867	45.6	11641	78.8	2631	17.3	799	5.3
$20,000-$34,999	3936	49.0	7045	89.4	1713	21.2	512	6.3
$35,000-$69,999	3849	47.3	7497	93.4	2140	26.2	639	7.8

Characteristic	Nicotine Use N=15,918		Alcohol Use N=28,907		Cannabis Use N=7,389		Cocaine Use N=2,259	
	N	%	N	%	N	%	N	%
≥ $70,000	1401	44.o	2977	94.8	925	28.9	313	9.8
Family income								
$0-$19,999	3996	48.4	6144	76.0	1375	16.5	479	5.7
$20,000-$34,999	3421	49.3	5748	84.7	1308	18.7	376	5.4
$35,000-$69,999	5002	47.2	9309	89.2	2385	22.4	717	6.7
≥ $70,000	3634	42.1	7959	93.5	2341	27.1	691	8.0
Marital Status								
Married	8536	45.5	16137	87.3	3865	20.5	1142	6.1
Divorced/separated	3217	56.4	5027	89.6	1503	26.8	525	9.1
Widowed	1533	45.7	2290	71.0	125	3.7	30	0.9
Never married	2767	41.9	5706	87.9	1916	28.9	566	8.5
Employment status								
Never employed	2542	47.0	3803	72.3	381	7.0	118	2.2
Ever employed	13511	46.6	25357	88.8	7028	24.1	2145	7.4

Note: NH/PI=Native Hawaiians or other Pacific Islanders and AI/AN=American Indians or Alaskan Natives

Drug Alcohol Depend. Author manuscript; available in PMC 2012 May 1.

Table 2

Psychopathologic and substance use-related characteristics of individuals with lifetime history of nicotine, alcohol, cannabis and cocaine use. Weighted percentages.

Characteristic	Nicotine Use N=15,918		Alcohol Use N=28,907		Cannabis Use N=7,389		Cocaine Use N=2,259	
	N	%	N	%	N	%	N	%
Any lifetime psychiatric disorder								
No	11458	27.4	21406	76.3	4573	5.1	1265	0.6
Yes	4595	58.0	7754	91.9	2836	31.0	998	10.0
Any lifetime mood disorder								
No	11458	44.5	21406	88.9	4573	17.7	1265	4.9
Yes	4595	53.0	7754	90.1	2836	32.5	998	11.4
Any lifetime anxiety disorder								
No	10544	44.2	19852	84.9	4328	18.0	1251	5.2
Yes	5509	52.2	9308	89.1	3081	29.0	1012	9.54
Any lifetime personality disorder								
No	11772	44.1	22186	84.8	4651	17.3	1229	4.6
Yes	4281	55.4	6974	91.3	2758	35.5	1034	13.3
Any lifetime conduct disorder								
No	15878	46.6	28864	86.2	7293	21.3	2232	6.5
Yes	175	54.2	296	92.5	116	35.8	31	9.6
Any lifetime psychotic disorder								
No	14945	46.4	27387	86.4	6866	21.2	2051	6.3
Yes	673	56.6	992	84.7	332	27.6	135	11.2
Any lifetime diagnosis of ADHD								
No	15533	46.2	28424	86.1	7031	20.8	2113	6.3
Yes	520	65.0	736	92.8	378	46.9	150	18.7
Any lifetime diagnosis of nicotine dependence								
No	8580	31.9	21996	83.4	4221	15.6	1096	4.1
Yes	7473	100.0	7164	96.3	3188	42.3	1167	15.5
Any lifetime diagnosis of alcohol dependence								
No	12547	42.5	24291	83.9	4672	15.7	1104	3.7

Characteristic	Nicotine Use N=15,918		Alcohol Use N=28,907		Cannabis Use N=7,389		Cocaine Use N=2,259	
	N	%	N	%	N	%	N	%
Yes	3506	71.8	4869	100.0	2737	55.8	1159	23.6
Any lifetime diagnosis of cannabis dependence								
No	15595	46.1	28608	86.0	6845	20.1	1960	5.8
Yes	458	81.8	552	98.9	564	100.0	303	53.9
Any lifetime diagnosis of cocaine dependence								
No	15707	46.2	28767	86.1	7032	20.6	1865	5.5
Yes	346	87.2	393	99.0	377	94.5	398	100.0
Any lifetime Substance Use Disorder (SUD)[a]								
No	7922	35.4	20198	82.3	1442	7.2	165	0.8
Yes	8131	67.7	8962	96.6	5967	40.7	2098	14.1
Family history of SUD[a]								
No	8466	41.5	16785	84.1	3313	16.1	840	4.1
Yes	7587	54.1	12375	89.2	4096	29.1	1423	10.1
Specific SU onset								
Before age 14	4974		2092		1051		51	
At/after age 14	11079		27068		6339		2208	

Use onset for the substance of interest described in the column (i.e. nicotine, alcohol, cannabis or cocaine)

[a]SUD for 10 substances included in AUDADIS IV (Sedatives, tranquilizers, painkillers, stimulants, cannabis, cocaine or crack, hallucinogens, inhalants/solvents, heroin, other) and alcohol and nicotine. The substance of interest described in the column (i.e. nicotine, alcohol, cannabis or cocaine) was excluded from the list

Table 3

Predictors of transition from first use to dependence on nicotine, alcohol, cannabis and cocaine among specific substance users. Univariate discrete-time survival analyses.

Characteristics	Nicotine Dependence N=7,320 HR (95%CI)	Alcohol Dependence N=4,822 HR (95%CI)	Cannabis Dependence N=529 HR (95%CI)	Cocaine Dependence N=376 HR (95%CI)
Gender (male)	0.88 (0.8-0.9)	1.89 (1.8-2.0)	1.39 (1.1-1.7)	0.79 (0.6-1.0)
Age group				
18-29	15.46 (13.9-17.2)	6.68 (5.9-7.6)	5.37 (3.9-7.4)	1.97 (1.4-2.9)
30-44	4.59 (4.2-5.0)	2.93 (2.7-3.2)	2.67 (2.0-3.6)	1.35 (1.0-1.8)
>45*	1.0	1.0	1.0	1.0
Race/ethnicity				
Whites*	1.0	1.0	1.0	1.0
Blacks	1.07 (0.9-1.2)	0.91 (0.8-1.0)	1.27 (0.9-1.7)	2.05 (1.5-2.8)
Hispanics	0.99 (0.9-1.1)	1.09 (0.9-1.3)	1.23 (0.9-1.7)	1.34 (0.9-1.9)
NH/PI	1.19 (0.9-1.5)	0.74 (0.6-1.0)	2.4 (1.2-4.8)	1.57 (0.6-4.2)
AI/AN	1.55 (1.3-1.8)	1.45 (1.2-1.8)	2.02 (1.2-3.3)	1.82 (0.9-3.7)
Urbanicity (Urban)	1.0 (0.9-1.09)	1.02 (0.9-1.1)	1.2 (0.8-1.6)	0.99 (0.7-1.4)
US-Born	1.41 (1.2-1.6)	1.7 (1.5-2.0)	0.75 (0.4-1.4)	1.09 (0.6-2.1)
Education (years)	1.0 (0.99-1.0)	0.99 (0.9-1.0)	0.89 (0.8-0.9)	0.85 (0.8-0.9)
Individual income				
$0-$19,999	1.39 (1.3-1.6)	1.23 (1.1-1.4)	2.77 (1.8-4.2)	2.76 (1.7-4.5)
$20,000-$34,999	1.39 (1.2-1.6)	1.35 (1.2-1.6)	2.16 (1.4-3.4)	1.97 (1.2-3.4)
$35,000-$69,999	1.25 (1.1-1.4)	1.27 (1.1-1.5)	1.33 (0.8-2.1)	1.61 (0.9-2.7)
≥ $70,000*	1.0	1.0	1.0	1.0
Family income				
$0-$19,999	1.09 (0.9-1.2)	1.38 (1.2-1.5)	2.4 (1.7-3.5)	2.25 (1.6-3.3)
$20,000-$34,999	1.03 (0.9-1.1)	1.16 (1.0-1.3)	2.36 (1.6-3.4)	2.14 (1.4-3.2)
$35,000-$69,999	1.05 (0.9-1.1)	1.19 (1.1-1.3)	1.41 (1.0-1.9)	1.45 (1.0-2.1)
≥ $70,000*	1.0	1.0	1.0	1.0
Marital Status				
Married/living with someone*	1.0	1.0	1.0	1.0
Never married	2.69 (2.5-2.9)	2.64 (2.4-2.9)	2.44 (1.9-3.1)	1.15 (0.8-1.6)
Divorced/Separated/Widowed	0.97 (0.9-1.1)	1.05 (0.9-1.2)	1.59 (1.2-2.1)	1.34 (1.1-1.8)
Ever employed*	1.0	1.0	1.0	1.0
Employment status (Never employed)	0.36 (0.3-0.4)	0.31 (0.3-0.4)	0.8 (0.5-1.3)	1.55 (1.1-2.3)
Diagnosed with a mood disorder	2.06 (1.9-2.2)	2.47 (2.3-2.7)	3.29 (2.6-4.2)	2.92 (2.3-3.8)
Diagnosed with an anxiety disorder	1.90 (1.8-2.0)	2.06 (1.9-2.2)	2.73 (2.2-3.5)	2.53 (2.0-3.3)
Any lifetime personality disorder	2.17 (2.0-2.3)	3.03 (2.8-3.3)	4.21 (3.3-5.4)	3.58 (2.8-4.6)
Any lifetime conduct disorder	1.34 (1.1-1.7)	1.58 (1.2-2.1)	1.81 (0.9-3.4)	1.11 (0.4-3.0)
Any lifetime psychotic disorder	1.38 (1.2-1.6)	1.53 (1.3-1.8)	1.91 (1.2-3.0)	1.78 (1.2-2.6)
Any lifetime diagnosis of ADHD	2.14 (1.9-2.4)	3.01 (2.6-3.5)	2.69 (2.0-3.7)	2.63 (1.8-3.9)

Characteristics	Nicotine Dependence N=7,320 HR (95%CI)	Alcohol Dependence N=4,822 HR (95%CI)	Cannabis Dependence N=529 HR (95%CI)	Cocaine Dependence N=376 HR (95%CI)
Diagnosed with nicotine dependence		3.52 (3.3-3.8)	2.99 (2.3-3.9)	2.74 (2.0-3.7)
Diagnosed with alcohol dependence	3.05 (2.9-3.2)		4.24 (3.3-5.4)	3.32 (2.5-4.5)
Diagnosed with cannabis dependence	4.31 (3.8-4.8)	7.39 (6.5-8.4)		3.83(3.0-5.0)
Diagnosed with cocaine dependence	3.08 (2.7-3.5)	6.64 (5.9-7.5)	6.33 (4.9-8.1)	
Family history of SUD	1.31 (1.2-1.4)	1.77 (1.7-1.9)	1.60 (1.3-2.0)	1.72 (1.3-2.2)
Specific SU onset (before age 14)	1.29 (1.2-1.4)	2.51 (2.3-2.7)	2.47 (2.0-3.1)	1.65 (0.9-3.0)

Note: NH/PI=Native Hawaiians or other Pacific Islanders and AI/AN=American Indians or Alaskan Natives

* Reference category

Table 4

Socio-demographic, psychopathologic and substance use-related predictors of transition from first use to Dependence on nicotine, alcohol, cannabis and cocaine among specific substance users. Multivariable discrete-time survival analyses.

Characteristics	Nicotine Dependence N=7,320 HR (95%C.I.)	Alcohol Dependence N=4,822 HR (95%C.I.)	Cannabis Dependence N=529 HR (95%C.I.)	Cocaine Dependence N=376 HR (95%C.I.)
Gender (Male)	0.9 (0.8-0.9)	1.93 (1.8-2.1)	1.44 (1.1-1.9)	
Age group				
18-29	15.78 (13.9-17.9)	3.85 (3.4-4.4)	3.09 (1.9-4.9)	
30-44	4.23 (3.9-4.6)	2.12 (1.9-2.4)	2.46 (1.7-3.5)	
≥45*	1.0	1.0	1.0	
Race/ethnicity				
Whites*	1.0	1.0	1.0	1.0
Blacks	0.96 (0.9-1.1)	0.89 (0.8-0.9)	1.18 (0.9-1.6)	3.45 (2.2-5.3)
Hispanics	0.80 (0.7-0.9)	1.08 (0.9-1.2)	0.82 (0.5-1.2)	1.19 (0.7-1.9)
NH/PI	1.29 (1.0-1.7)	1.02 (0.7-1.5)	2.31 (0.8-6.7)	2.33 (0.6-8.7)
AI/AN	1.3 (1.1-1.5)	1.05 (0.8-1.3)	1.91 (1.2-3.0)	1.79 (0.6-5.3)
US-Born	1.35 (1.2-1.6)	1.55 (1.3-1.9)		
Education years (continuous)	0.98 (0.9-1.0)			
Marital Status				
Married/living with someone*	1.0	1.0		1.0
Never married	1.33 (1.2-1.5)	1.84 (1.6-2.1)		1.07 (0.6-1.8)
Divorced/Separated/Widowed/	1.32 (1.2-1.4)	2.29 (2.0-2.6)		1.86 (1.1-3.3)
Employment status (Never employed)	0.49 (0.4-0.6)	0.54 (0.5-0.6)		
Diagnosed with a mood disorder	1.62 (1.4-1.8)	2.29 (2.0-2.6)	2.69 (1.9-3.9)	2.58 (1.5-4.4)
Diagnosed with an anxiety disorder	1.96 (1.8-2.2)	1.98 (1.7-2.3)	2.31 (1.6-3.4)	
Any lifetime personality disorder	1.42 (1.3-1.5)	1.64 (1.5-1.8)	2.3 (1.7-3.1)	1.99 (1.4-2.9)
Any lifetime psychotic disorder	1.17 (1.0-1.3)			1.46 (0.9-2.5)
Diagnosed with nicotine dependence		3.29 (2.9-3.7)	2.06 (1.4-3.1)	
Diagnosed with alcohol dependence	2.35 (2.1-2.6)		2.55 (1.8-3.5)	2.56 (1.7-3.8)
Diagnosed with cannabis dependence	1.66 (1.2-2.3)	2.99 (2.3-3.9)		3.84 (1.8-8.2)
Diagnosed with cocaine dependence	1.44 (1.0-2.1)	3.27 (2.1-5.2)	4.14 (2.3-7.6)	
Family history of SUD	1.14 (1.1-1.2)	1.49 (1.4-1.6)		
Specific SU onset (before age 14)	1.13 (1.1-1.2)		0.63 (0.5-0.9)	0.34 (0.1-0.9)

*Reference categories