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Different lengths of times for progressions in adolescent substance involvement

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Abstract

The present study examined Lengths Of Times for important transitions in substance involvement from Initiation to Regular use (LOTIR), first Problem from drug use (LOTIP), and first experience of Dependence (LOTID) for alcohol, tobacco, cannabis, cocaine, and opiates. Data were from a longitudinal study of 590 children (22.2% female) at different levels of risk for substance use disorders based on their fathers' substance use-related diagnoses. Participants' substance involvement was assessed at four ages: 10-12, and follow-ups at two, five, and eight years later. Results suggested that faster transitions were more due to drug-related constructs (including possible social milieus of different drug classes and interactions between drug class and neurophysiology) than intrapersonal constructs. The shortest transition times (and greatest addictive liabilities) were for opiates followed respectively by cocaine, cannabis, tobacco, and alcohol. Females had shorter transition times, though gender differences were small. Some evidence was found for a familial influence on transition times above what was accounted for by differences between substances.

Keywords

Adolescence; Drug abuse; Regular use; Gender; Alcohol; Tobacco; Cannabis

1. Introduction

Several realms of addiction research have converged on the need for novel phenotypes of pathological substance use. These realms of addiction research include genetic research, clinical diagnostic nomenclature (Hasin & Grant, 2004; Langenbucher et al., 2004; Ridenour, Cottler, Compton, Spitznagel, & Cunningham-Williams, 2003), abuse/addictive liability drug research (Ator & Griffiths, 2003; Balster & Bigelow, 2003; Fischman & Foltin, 1991; Griffiths, Bigelow, & Ator, 2003; Ridenour, Maldonado-Molina, Compton, Spitznagel, & Cottler, 2005), and efforts to provide translational interpretations of animal research to people (Ahmed & Koob, 1998; Deroche-Gamonet, Belin, & Piazza, 2004; Vanderschuren & Everitt, 2004). The quality and type of research that can be conducted are limited by measures available. Novel addiction phenotypes that not only advance specific realms of addiction research but also simplify the cross-informing between realms could accelerate scientific and translational advancements.

1.1. Length of time for transition to greater substance involvement

One phenotype with potential utility for genetic, clinical, addictive liability (risk for addiction), and translational addiction research is the speed at which substance users progress from mild

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to more severe involvement (Chen & Anthony, 2004; Ridenour et al., 2003, 2005; Wagner & Anthony, 2002). In theory, substances with greater addictive liabilities will generate faster progressions from initiation to greater involvement (e.g., regular use). Differences in the average times of progressions in users of different substances (e.g., alcoholics vs. cocaine addicts) appear to parallel animal findings on addictive liability (Ridenour et al., 2003, 2005). Faster progressions have been observed for women compared to men (consistent with animal studies on addictive liability) and early initiators compared to later initiators of substance use (consistent with human studies on addictive liability) (Ridenour et al., 2005).

What benefits might be realized from a human addiction liability phenotype that parallels animal models? Consider the growing evidence for a common liability to addiction across all substances from neurobiology (e.g., dopamine mediated reward neural circuitry, Koob & Le Moal, 2001; Nestler 2004, 2005) and psychiatric epidemiology (e.g., behavior genetics and neurobehavioral disinhibition; Agrawal, Neale, Jacobson, Prescott, & Kendler, 2005; Agrawal, Neale, Prescott, & Kendler, 2004; Clark, Cornelius, Kirisci, & Tarter, 2005; Iacono, Carlson, Taylor, Elkins, & McGue, 1999; Kirisci, Tarter, Vanyukov, Reynolds, & Habeych, 2004; Tarter et al., 2003, 1999; Tsuang et al., 1998; Vanyukov et al., 2003). Theoretical underpinnings of neural substrates that mediate common addictive liability rely heavily on animal studies (Nestler, 2004). Research of a common addictive liability model in people to date largely has relied on observational or self-report measures (as opposed to *en vivo* studies of neural functioning). A significant challenge to translating the genetic and neurobiological findings from animal studies on addiction to people is to identify endophenotypes for those mechanisms.

In addition to the common addiction liability model, animal studies and addictive liability research on people's subjective experiences of drug effects document that drugs have unique impacts on separate neural mechanisms (Boehm et al., 2004; Dani, Ji, & Zhou, 2001; Jones, Johnson, Fudala, Henningfield, & Heishman, 2000; Kreek, 2001; Le Foll, Sokoloff, Stark, & Goldberg, 2005; Schulze & Jones, 1999; Smith, Jones, & Griffiths, 2001; Volkow, Fowler, Wang, & Swanson, 2004). Less progress has occurred in elucidating the mechanisms of drug-specific effects in people and little research has been conducted to integrate the common addiction liability model with drug-specific effects in people. Specific genotypes are likely to be implicated in the subjective experiences and neurobiological effects of one drug versus another. If a phenotype in people is found to parallel addictive liability studies in animals, it could accelerate the transfer of knowledge from animals to people (e.g., used in genetic association studies). Moreover, a phenotype that gauges drug-related constructs' contributions to addiction liability could be used to integrate drug-specific liability with the common addiction liability model as well as parse the contributions to overall addiction liability of drug-related constructs, intrapersonal characteristics, and environmental variables (Ridenour et al., 2005).

Previous studies suggest that average lengths of times for transitions between levels of drug involvement gauge drug-related constructs. In a sample consisting mostly of addicts, none of the differences between drugs in users' mean times for transitions was accounted for by gender or age of initiation (Ridenour et al., 2005). Also, times for transitions from abuse to dependence did not correlate between drugs (Ridenour et al., 2003). However, these studies of progression speeds for different drugs had a number of limitations (Ridenour et al., 2003, 2005). Data were retrospective. DSM abuse and dependence diagnoses were used as phenotypes (shortcomings of which are detailed later). Phenotypes did not align closely with the animal studies to which results were compared. Samples were limited to mostly adult addicts. Improvement on these limitations would strengthen the validity of progression rate differences between substances.

1.2. Addictive liability of substances as a source for phenotypes

A related arena of animal research on substance addiction is the abuse liability of drugs (Ator & Griffiths, 2003; Balster & Bigelow, 2003; Griffiths et al., 2003). Abuse liability research on animals and people has clarified how certain substances can lead to drug use-related disorders, informed Food and Drug Administration policy, and clarified the relative potential of different drugs to generate addiction in consumers. Abuse liability research has been limited by (a) primarily testing substances developed by pharmaceutical manufacturers (e.g., not including inhalants), (b) conducting research in laboratory settings that do not resemble “street” use, and (c) techniques that are difficult to adapt to large-sample, epidemiological and clinical research. Although “abuse liability” is the term used in recent literature, the term “addictive liability” is used here because abuse refers to a specific diagnosis that was used in analyses. “Addictive liability” is used also to highlight the transition towards addiction. The properties that make a substance reinforcing may not be fully homologous with factors that lead toward abuse or dependence. Indeed, animal research focused on behavioral changes thought to reflect the process of dependence and not simply reinforcement (e.g., Deroche-Gamonet et al., 2004) suggests these processes are best conceptualized as distinct phenotypes.

The addictive liability of drugs is not only a result of constructs related to the drugs, but also from interactions between drug and individual characteristics (e.g., physiological or subjective experiences). Part of addictive liability is likely due to an interaction between genotypes and drug characteristics, which generate pleasurable or unpleasant physiological responses (Cook et al., 2005; Mulligan et al., 2003; Oslin et al., 2003), as well as environmental factors that may moderate whether drug consumption is reinforcing (Carroll, France, & Meisch, 1979; Ellenbroek, van der Kam, van der Elst, & Cools, 2005). Clarification of genetic contributions to ontology of addiction could be greatly advanced if the addictive liability of substances could be studied in terms of the contributions of genotypes, other interpersonal characteristics, environmental factors, and the interactions between them. A technique for studying humans’ addictive liability has been preliminary tested using Diagnostic and Statistical Manual-IV (DSM-IV) diagnoses of abuse and dependence (Ridenour et al., 2005). However, shortcomings of DSM-IV diagnoses limit the validity and utility of this technique.

1.3. Obstacles of human addiction diagnostic phenotypes

To maximize translation of animal research to people, the optimal phenotypes of human pathological substance use could be observable in animals. For obvious reasons, most animal studies quantify substance use in terms of amount of self-administration of a drug and observable behavior (Brebner, Froestl, Andrews, Phelan, & Roberts, 1999; Stafford, LeSage, & Glowa, 1998). Human addiction is complex, which results in complex diagnostic phenotypes. DSM-IV abuse and dependence utilize complex phenotypes, such as an individual’s social dysfunction within his or her environment due to substance use (APA, 1994). Moreover, the same substance use diagnosis could encompass heterogeneous subgroups because different subsets of criteria qualify for diagnosis.

These and additional shortcomings of DSM-IV abuse and dependence criteria restrict their utility in people, much less their utility for comparisons between people and animals. DSM-IV nomenclature suggests that abuse should occur before dependence (pertaining to the same drug) and that only a subset of persons who experience abuse should advance to experience dependence (APA, 1994). Both of these expectations regarding the association between abuse and dependence diagnoses have been refuted empirically (Hasin & Grant, 2004; Hasin, Van Rossem, McCloud, & Endicott, 1997; Ridenour et al., 2003; Schuckit et al., 2001). Ridenour et al. (2003) argued that the environmental element of each abuse criterion makes them impure measures of individuals’ drug misuse. To illustrate, the criterion of use leading to social problems can be avoided by socializing only with persons who misuse substances or do not

view drug use as problematic. Large differences exist between drugs in how abuse and dependence diagnoses and criteria are associated, even though the same DSM criteria are used (Langenbucher et al., 2004). Sizable proportions of individuals experiencing pathological substance use do not meet criteria for diagnosis and their plight can go undetected (Hasin & Paykin, 1999; Pollock & Martin, 1999; Sarr, Bucholz, & Phelps, 2000).

1.4. Attempts to develop animal models that align with human addiction

Recent animal models of human addiction have increased in their sophistication to imitate DSM criteria. One animal model of human addiction consisted of increased drug self-administration, based on the fact that substance ingestion increases from initiation to addiction (Ahmed & Koob, 1998). A more recent animal model was based on continued use of a drug in spite of environmental adversity associated with drug use (Vanderschuren & Everitt, 2004). Validity for this model was demonstrated in that rats with limited self-administration of cocaine desisted use of cocaine when conditioned stimuli signaling footshock were present whereas rats with longer self-administration history continued cocaine use despite this signaled adversity. A third animal model used three separate criteria: persistence of drug seeking when the animal was signaled that the drug was not available, willingness to spend great amounts of time and effort to get the drug (using a progressive-ratio, break-point design), and continued drug use when self-administration of the drug also resulted in receiving a shock “punishment” (Deroche-Gamonet et al., 2004). The validity of this three-criterion model of rat addiction was demonstrated using a number of tests. A notable result was the large individual differences in whether cocaine dependence emerged even though all of the animals readily self-administered the drug.

1.5. Potential human behavioral phenotypes of addiction that align with animal models

Behavioral indicators of pathological substance use (e.g., bingeing, frequency, and quantity) correlate highly with substance use-related disorders (Canagasaby & Vinson, 2005; Chen, Kandel, & Davies, 1997; Hill, White, Chung, Hawkins, & Catalano, 2000). It appears that a lower threshold of frequency and quantity of use is associated with dependence in adolescents compared to adults (Chen et al., 1997). Adolescent animals also appear to experience greater addictive liability with the same amount of use as their adult counterparts (Fernandez-Vidal, Spear, & Molina, 2003; Philpot, Badanich, & Kirstein, 2003; Vastola & Douglas, 2002). These parallel results in addictive liability between animals and people suggest that behavioral phenotypes might provide a bridge for translation of animal research to people. They also suggest that addictive liability research on drug types may not generalize between adolescents and adults.

Recent item response theory analyses of addiction treatment patients identified specific DSM-IV criteria associated with varying severities of addiction to alcohol, cannabis, and cocaine (Langenbucher et al., 2004). Although individual criteria were associated with different levels of addiction severity for different drugs, one criterion (use of the drug in spite of knowing that a physical or psychological problem is caused by use) was associated with relatively mild addiction for all three substances. Another criterion (important activities given up or reduced because of drug use) was associated with relatively severe addiction for all three substances. Animal models of these specific criteria already have been demonstrated to be valid (Deroche-Gamonet et al., 2004; Vanderschuren & Everitt, 2004).

1.6. Purposes of the present study

The present study was conducted partly to test behavioral phenotypes as measures of drug-related addictive liability using speed from initiation of use to greater substance involvement. Useful behavioral phenotypes would (a) consist of observable behavior to facilitate translational research from animal models to people, (b) reflect clinically significant substance

misuse, and (c) occur prior to diagnostic levels of addiction. Animal studies suggest that opiates and cocaine have the greatest addictive liabilities followed by cannabis and then alcohol (Erdtmann-Vourliotis, Mayer, Riechert, & Voker Holtt, 1999; Stafford et al., 1998; Winger, Young, & Woods, 1983). Hence, if the lengths of times for transitions of different drugs in humans were consistent with animal studies, the fastest transitions would occur for opiates and cocaine, followed respectively by cannabis, and alcohol. How nicotine falls into the rank order of addictive liabilities is less clear and was explored in the present study. Over the lifetime, the prevalence of dependence in persons who ever used a substance is greatest for tobacco compared to other substances (Anthony, Warner, & Kessler, 1994; Kandel, Chen, Warner, Kessler, & Grant, 1997). Whereas nearly all persons who smoke during adulthood initiate smoking before age 18 (USDHHS, 1994), the prevalence of tobacco dependence among users increases sizably from adolescence to early adulthood (Anthony et al., 1994; Breslau, Johnson, Hiripi, & Kessler, 2001; Kandel et al., 1997). The final purpose to this study was to test for associations between addictive liability as measured by speed of transitions and parental substance use-related diagnoses. Numerous studies have demonstrated that offspring of parents with an addiction are at increased risk for addiction to many drugs (Bierut et al., 1998; Merikangas et al., 1998; Nurnberger et al., 2004). Genetic and environmental risks appear to be common to use, abuse, and dependence for many addictive substances (Agrawal et al., 2004; Tsuang et al., 1998).

2. Methods

2.1. Participants

Participants were 590 youth (i.e., index cases or offspring) who were identified, recruited, and initially assessed in late childhood (ages 10 through 12 years, mean=11.48 years, SD=0.91) by contacting their biological fathers (i.e., probands). Recruitment occurred through multiple sources, including addiction and other psychiatric treatment programs, social service agencies, newspaper and radio advertisements, and a sampling frame purchased from a marketing firm. Proband fathers fell into three subgroups: those with a history of a DSM-III-R (American Psychiatric Association, 1987) substance use disorder ($n=232$), those with neither substance use nor any other major psychiatric disorder ($n=293$), versus those with a history of psychiatric disorder other than a substance use disorder ($n=65$). This longitudinal family study was ideal for the research questions posed in this study. A disproportionately large number of the child participants developed substance use-related problems; yet, a comparative sample that more closely resembles the general population was included. This high-risk, longitudinal family design provided an enriched dataset that avoided the prohibitive costs that would be required to obtain similar data by sampling the general population.

Participants were 22.2% female, with similar proportions of females in each of the recruitment statuses: 20.26% of participants with a father with a substance use disorder, 22.18% of participants with fathers having no psychiatric history, and 29.23% of participants with fathers having a psychiatric disorder other than a substance use disorder (not a statistically significant difference, $p = 0.31$). (Note that the CEDAR study design called for a higher proportion of male than female index cases.) Index children from the three groups of proband fathers also did not differ regarding age of baseline assessment. Participants who were in the longitudinal study long enough to participate in the fourth wave (ages 18 to 20) were included in the present study.

Consistent with prior studies documenting an association between socioeconomic status (SES) and adult SUDs (Dohrenwend, Levav, Shrout, Schwartz, Naveh, Link, Skodol, & Stueve, 1992), families with fathers having a substance use-related disorder, compared to other families, had significantly lower SES by Hollingshead two-factor index (Hollingshead,

1990). Families with addicted fathers also had higher proportion of African American families. Subsequent analyses controlled for these differences where appropriate.

2.2. Procedures

The assessments reported here were components of a more extensive, substance use research protocol implemented at CEDAR (Clark, Pollock, Mezzich, Cornelius, & Martin, 2001; Tarter & Kirisci, 2001). The primary objective of this ongoing study is to employ a prospective research design to understand the etiological pathways to substance use disorders. In addition to that (ages 10 through 12), data from three follow-up assessments (ages 12 to 14, 15 to 17, and 18 to 20) were included.

2.3. Measures

2.3.1. Substance use—Participants' substance use was assessed with a diachronic technique developed for the CEDAR studies to longitudinally track levels of involvement (Clark et al. 2001, 2005). During baseline and follow-ups, participants were asked whether they had used any of a list of substances, including tobacco, alcohol, cannabis, cocaine, and opiates. For each substance that a participant used, onset dates within a month of accuracy were assessed for initiation, regular use (defined as at least one use per month during a phase of consumption), first occurrence of problem due to substance use (defined as the first experience of a DSM-III-R abuse or dependence criterion), and first occurrence of DSM-III-R substance use-related dependence (using the Structured Clinical Interview for Diagnosis; Spitzer, Williams, & Gibbon, 1988).

Except for tobacco, substance-related problems and diagnoses were based on DSM-III-R nomenclature because it was the latest DSM edition at the initiation of the study (APA, 1987). The manner in which DSM-III-R substance use criteria were analyzed resembles results that would be found using DSM-IV criteria because the same criteria were used in the two nomenclatures but reassigned to the abuse and dependence diagnoses. Reliability and validity of the Structured Clinical Interview for Diagnosis for use with adolescents have been reported to be good to excellent for diagnoses as well as subclinical symptomatology (Bailey, Martin, Lynch, & Pollock, 2000; Martin, Pollock, Bukstein, & Lynch, 2000). Martin et al. (2000) have demonstrated that dates of onset can be reliably assessed for symptoms as well as diagnoses in adolescents using the Structured Clinical Interview for Diagnosis. Clark, Kirisci, & Moss (1998) demonstrated that consumption of alcohol in amounts less than one standard drink (e.g., "even just a sip") neither consistently indicates problematic use nor predicts substance use-related problems. Hence, alcohol initiation was the first consumption of one standard drink of alcohol. Initiation for other substances was the first consumption of any amount. Opiates consisted of either "street" forms or prescription forms.

Parental diagnoses related to substance use were assessed using the Structured Clinical Interview for Diagnosis based on DSM-III-R nomenclature. Participants' parents were screened for use of all substances; diagnostic criteria were assessed for the most frequently used classes of substances using a consensus conference and the best estimate diagnostic procedure (Clark et al., 2001, 1997, 1998).

DSM substance use-related diagnoses do not include abuse for tobacco (APA, 1994, 1987). Rather than restrict tobacco to only dependence criteria (and thereby bias tobacco results), results from the Fagerstrom Test for Nicotine Dependence (Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991) also were used as measures of pathological use of tobacco. Scores of 1 or greater on the Fagerstrom were considered indicative of a substance use-related problem for transitions analyses.

2.3.2. Lengths of times for transitions—Transitions were measured in Lengths Of Times from Initiation to either Regular use (LOTIR), first experience of a Problem related to substance use (LOTIP), or the first time that Dependence criteria were experienced for at least one month (LOTID). Ages of initiation and first experience of regular use, problem due to substance use, and dependence were assessed and analyzed to the nearest month of onset.

2.4. Data analyses

Data analyses proceeded in several steps, using SAS release 8.2 (SAS, 2001), with results from earlier steps used to inform how later analyses were conducted. First, the lengths of times for transitions were estimated for tobacco, alcohol, cannabis, cocaine, and opiates. Second, survival curve analyses of transitions were conducted separately for the three most commonly used substances (tobacco, alcohol, and cannabis) to examine data descriptively in a manner that accounted for the right-censored and event-occurrence nature of these variables. Third, where sample sizes permitted, mean differences in lengths of times for transitions between males and females were tested using one-way ANOVA. Fourth, mean differences in LOTIR and LOTIP were tested for participants who eventually report substance use dependence versus not using one-way ANOVA. Fifth, two tests were conducted in attempt to statistically account for differences between drugs in the lengths of times for transitions. To estimate the degree to which personal characteristics contribute to speeds of transitions, correlations between drugs' LOTIRs, LOTIPs, or LOTIDs were estimated using Kendall's Tau and Proc Corr. Finally, multiple regression analyses (using Proc GLM) were conducted to account for between-drug differences in the transition times using gender and number of parents with a diagnosis.

Traditionally, when multiple analyses are conducted, adjustments are made to statistical significance thresholds to account for the increased probability of Type I errors (Stevens, 1992). However, the present study was conducted with an emphasis on the practical significance of the findings (i.e., emphasis was on effect size) rather than the statistical significance, which has been demonstrated to provide more valuable information (Cohen, 1990,1994; Schmidt & Hunter, 2002). To balance the competing risks of Type I and II errors, unadjusted p-values are reported. Reporting unadjusted p-values permits readers who prefer to use threshold adjustments to compare observed p-values to the reader's preferred threshold p-value. Results meeting the $p < 0.05$ were interpreted herein as being statistically significant; results with $p < 0.10$ were considered trends.

3. Results

Table 1 presents sample sizes for each phenotype; means (and standard deviations) of age of initiation; and lengths of times between initiation and either regular use (LOTIR), first problem due to use (LOTIP), and early dependence (LOTID). Each length of time of progressions was right skewed. Medians also are presented, which better represent midpoints of the distributions.

Although a nearly equal proportion of initiators of tobacco and alcohol experienced regular use, only 28.6% of tobacco initiators experienced a problem due to tobacco use compared to 46.2% of alcohol initiators. This difference was not due to age of initiation because the mean and median ages of initiation of tobacco and alcohol use were nearly equal, as were the proportion of regular users of each substance. The proportion of alcohol users that experienced a problem due to alcohol use resembled results for users of illicit drugs (40% to 50%).

3.1. Overall substance differences in lengths of times for transitions

Results presented in Table 1 were consistent with the a priori hypothesis that the lengths of times for transitions would be slowest for alcohol followed, respectively, by tobacco, cannabis, cocaine, and opiates. However, the median LOTIR for each substance was zero months and

inspection of the survival curves suggests little differences in LOTIRs for alcohol, tobacco, and cannabis (Fig. 1). The median LOTIP for each substance was 24.00 for alcohol, 12.00 for tobacco, and 0.00 for cannabis, cocaine, and opiates. Inspection of survival curves suggests that LOTIP was longest for tobacco followed by alcohol and then cannabis (Fig. 2). These results were mostly consistent with a priori hypotheses. A rank order similar to LOTIP was found in the median LOTIDs: 36.00 for alcohol, 12.00 for tobacco, 24.00 for cannabis, and 0.00 for cocaine and opiates. Survival curve inspection suggested that LOTID was longest for tobacco followed by alcohol and then cannabis (Fig. 3).

Other results presented in Table 1 were inconsistent with the notion that transition times gauge addictive liability of different substances. The proportions of substance users who later experienced regular use were greatest for tobacco (79.1%) and alcohol (79.8%), followed by cannabis (66.1%), cocaine (54.6%), and opiates (55.3%), which was the reverse order of the lengths of times for transitions. The proportions of substance initiators who progressed to experiencing a problem or dependence were consistent with the speed of transitions.

3.2. Gender differences in lengths of times for transitions for tobacco, alcohol, and cannabis

Consistent with previous reports of length of time for transitions in people and abuse liability animal studies (Ridenour et al., 2005), females' mean lengths of times for transitions were shorter than males', except for the cannabis LOTIR (Table 2). Median of times for transitions was equal between females and males (0.00) for tobacco and cannabis LOTIRs. Female's LOTIPs were shorter than males for tobacco ($p = 0.08$, a trend) and alcohol ($p = 0.05$); female's LOTIP also was shorter for cannabis, but only 24 females experienced a problem related to use of cannabis. In contrast to the faster transitions experienced by females (implying support for transition times gauging addictive liability of substances), more males experienced problems and dependence related to use of each substance compared to females. The numbers of cocaine and opiate users were too small to test for gender differences.

3.3. Lengths of times for transitions and substance diagnoses

Table 3 presents associations between LOTIR or LOTIP and whether a participant later met criteria for a diagnosis related to use of the same substance for tobacco, alcohol, or cannabis. For alcohol and tobacco, participants who later experienced a diagnosis related to those substances had slightly faster LOTIRs and LOTIPs (this was true regarding cannabis only for LOTIR). However, statistical significance was not reached for any of the analyses, in part due to (a) few participants who experienced a substance use-related diagnosis and (b) large variances for LOTIR and LOTIP. The difference in alcohol LOTIR between participants who experienced dependence versus those who did not (the analysis with the greatest "n" size) reached a trend level of statistical significance ($p = 0.06$).

3.4. Correlations between the lengths of times of transitions for different substances

LOTIRs for alcohol and cannabis were significantly correlated ($\tau = 0.20$, $p = 0.001$, $n = 204$), as were LOTIRs for alcohol and tobacco ($\tau = 0.12$, $p = 0.04$, $n = 204$). For LOTIPs, only tobacco and cannabis correlated significantly ($\tau = 0.23$, $p = 0.05$, $n = 52$). LOTIDs for alcohol and cannabis were significantly correlated ($\tau = 0.25$, $p = 0.005$, $n = 32$). All other LOTID correlations had "n" less than 20. All correlations that included use of opiates or cocaine had insufficient sample sizes for correlational analyses ($n = 19$ or less).

3.5. Multiple regressions to account for between-drug differences

Three pairs of multiple regression analyses were conducted to (a) explore how much variability in LOTIR, LOTIP, and LOTID could be accounted for by drug type and (b) attempt to account for differences between drugs in times for progressions using gender and parental substance

disorders. Drug type accounted for 7% of LOTIR variance and differences between drugs were significant (Table 4). The proportion of LOTIR variance and beta weights associated with drug types changed little when gender, parental substance use disorders, and parental tobacco use disorders were added as predictors (Table 4). A trend was found for a 4.73 month shorter LOTIR among adolescents with two parents with a tobacco use disorder, controlling for the other LOTIR predictors ($p = 0.07$). Ten percent of LOTIP variance was accounted for by drug type (Table 5). Twelve percent of LOTIP variance was accounted for when gender and parental substance disorders were added as predictors (Table 5). Females experienced a 7.84 month shorter LOTIP on average compared to males. A trend was found for a 5.3 month shorter LOTIP associated with having two parents with a substance use disorder other than tobacco. After gender and parental substance use disorders were added as predictors, the LOTIPs of alcohol and tobacco were no longer statistically different. Twelve percent of LOTID variance was accounted for by drug types; tobacco and alcohol LOTIDs were not statistically different (Table 6). Results for LOTID prediction changed little when gender and parental substance use disorders were added as predictors (which were not statistically significant).

4. Discussion

Results were consistent with the hypothesis that lengths of times for transitions gauge the addictive liability of substances. The slowest transitions occurred with alcohol and tobacco, followed respectively by cannabis, cocaine, and opiates. Moreover, rank orders of times for transitions of substances were consistent regardless of which transition was studied. The results also suggested that times for transitions largely gauge the impact of drug-related constructs, perhaps including the social milieu in which a drug is used, on human substance involvement.

Previous retrospective studies were based on dissimilar samples, including mostly adult addicts and an epidemiological sample of the U.S. adult population. The present study utilized a different DSM nomenclature, a longitudinal design, and a sample of adolescents. Measures of transitions were broadened to consist of phenotypes that precede dependence. The present study also tested for diagnostic and familial associations with the speed in transitions.

4.1. Differences between substances

Differences between substances were consistent, regardless of the type of transition that was studied and were consistent with previous research on transitions in substance involvement (Ridenour et al., 2003, 2005; Wagner & Anthony, 2002). It appears that etiologies of the speeds of transitions differ in important ways between substances. Few of the Kendall's taus between LOTIRs, LOTIPs, or LOTIDs were statistically significant and none of the taus accounted for more than 7% of variance in the speed of a transition. Moreover, the etiologies of different transitions for the same substance also might differ in important ways. Results in Table 3 were consistent with the hypothesis that persons who eventually experience a substance-related diagnosis transition through levels of substance misuse faster than those who do not experience a diagnosis. However, differences between adolescents who later did and did not experience a diagnosis were very small and statistically nonsignificant, with a single trend noted for regular use of alcohol. These nonsignificant results may be partly due to the fact that participants have not passed entirely through the developmental period of greatest risk for substance addiction. These analyses should be repeated when later waves of the study have been completed. If the present findings are replicated, it would suggest that the different transitions (e.g., initiation, regular use, first problem) occur as a result of distinct etiological mechanisms.

4.2. Tobacco addictive liability

Previous studies in this line of research did not include tobacco. Overall, results of this study suggest the addictive liability of tobacco is greater than alcohol but lower than cannabis,

cocaine, and opiates. One finding contradicted the notion that the addictive liability of tobacco is greater than alcohol: about 1/2 of the proportion of tobacco users experienced dependence (8.45%) compared to 15.25% of alcohol users who experienced dependence. Similar prevalences of tobacco and alcohol users were found for experiencing problems associated with use. These seeming contradictory results may be partly due to reduced availability of tobacco compared to alcohol during adolescence. Lifetime prevalence of dependence in persons who ever used a substance is greatest for tobacco users compared to users of other drugs (Anthony et al., 1994; Kandel et al., 1997). Whereas nearly all persons who smoke during adulthood initiate smoking before age 18 (USDHHS, 1994), the prevalence of tobacco dependence among users increases greatly from adolescence to early adulthood (Anthony et al., 1994; Breslau et al., 2001; Kandel et al., 1997). Perhaps much greater exposure to tobacco is required to experience DSM-defined dependence compared to alcohol. Findings for tobacco may change with completion of later waves of the study from which data came. Perhaps refinements to the speed of transition metric might provide better estimates of the addictive liabilities of substances.

4.3. Refinement of gauging substances' addictive liability

The need for refinement to measuring speed of transition also was evidenced for substances other than tobacco. One result was inconsistent with the notion that the greatest addictive liability occurs for opiates and is lower, respectively, for cocaine, cannabis, tobacco and alcohol. The proportions of users of substances who later experienced regular use were greatest for tobacco and alcohol, followed respectively by cannabis, cocaine, and opiates (which was the reverse order observed for the lengths of times for transitions). It might be postulated that if one substance truly had a greater addictive liability than another substance, then a greater proportion of users of the former substance would increase their use of the substance. This postulate assumes that early and later stages of drug use are influenced by the same or highly-related etiological processes. At least part of the observed rank order of the proportions of users who increased their involvement with different substances could be due to the later initiations of the more addictive substances (because shorter time periods of use have occurred during which regular use, problems, or dependence could be experienced).

Perhaps the speed of transitions and the proportions of users who experience a transition could be combined to obtain a better estimate of the relative addictive liabilities of substances. A multidimensional technique might eventually be developed to gauge the distinct etiologies of proportion of users who advance to later stages and the speed of transitions. Another option might be to weight lengths of times for transitions by the proportion of initiators who experience the transition. This weighting might be computed for tobacco (using LOTIR from Table 1) as:

$9.59 \text{ (number of months from initiation to regular use)} \times 0.2095 \text{ (one minus the proportion of initiators who used regularly or } 1 - 0.7905) = 2.01$.

Using this formula for the regular use transition, the relative addictive liability for different drugs is: alcohol = 3.77, tobacco = 2.01, cannabis = 1.60, cocaine = 1.21, and opiates = 0.77. If these weightings were computed with dependence as the transition, alcohol = 32.58, tobacco = 28.48, cannabis = 23.97, cocaine = 3.41, and opiates = 1.18, the same rank order as addictive liability based on LOTIR. Although the rank orders are similar using LOTIP (tobacco = 16.00, alcohol = 15.28, cannabis = 6.65, cocaine = 1.71, and opiates = 0.9), the order of tobacco and alcohol was reversed. In general, the weighting of times for transitions by the proportion of users who experience a transition provided consistent rank orders of addictive liabilities of drugs.

4.4. Gender differences

Results of the present analyses, overall, were consistent with previous reports that the lengths of times for transitions are faster for females than for males. However, the observed differences between genders were not all statistically significant. For cannabis LOTIR, males' transition time was shorter, on average, than females'. Samples of females were often smaller than is preferred for tests of mean differences and gender differences for cocaine and opiates could not be tested because there were so few users. Gender differences in LOTIR, LOTIP, and LOTID were further tested, controlling for drug types and number of parents with substance dependence, using regression models (Tables 4 5 and 6). Results of regression models replicated the tests of mean differences. Females consistently had faster transitions, but statistical significance was found only with LOTIP (Table 5). One consideration is that the gender difference(s) apply only to persons who experience a drug use transition. If males' and females' times for transitions are weighted by the proportion of initiators who experience the transition, males' values were less than females' on average for tobacco, alcohol, and cannabis LOTIRs (1.8 vs. 2.5, 3.6 vs. 4.3, 1.3 vs. 2.0, respectively) whereas the reverse was true for LOTIPs (17.0 vs. 8.8, 15.5 vs. 12.4, 6.5 vs. 6.2, respectively). These results suggest that males' liability to regular use is greater, but liability to substance use problems is greater for females.

4.5. Diagnostic outcomes and times for transitions

It was hypothesized that a shorter time for transition would be associated with eventually experiencing a substance use-related diagnosis. Nearly all of the observed results in Table 3 are consistent with this hypothesis (the reverse was true for cannabis LOTIP, but only 15 users had experienced a diagnosis). However, none of the differences between users with a diagnosis versus users without a diagnosis were statistically significant (a trend was observed for alcohol, $p = 0.06$). The lack of statistical significance is due in part to not yet having follow-up data through early adulthood. If this finding is replicated when the sample matures through early adulthood, it would suggest that the reinforcing properties of substances alone do not determine whether someone experiences a substance use-related diagnosis. These preliminary results suggest that LOTIR may predict later diagnoses related to use of alcohol and cannabis.

4.6. Familiality of times for transitions

Regression models suggested that family history of drug or alcohol disorder or tobacco disorder is weakly associated with adolescents' times for transitions, controlling for drug-related constructs which probably include familial characteristics (Tables 4 5 and 6). Reinforcing effects of substances are not only due to drug characteristics. Rather, they result from the interaction between drug-related constructs and individuals' characteristics including genetic and environmental influences (Cook et al., 2005; Ellenbroek et al., 2005; Mulligan et al., 2003; Oslin et al., 2003). After controlling for drug types and gender, two trends for familial associations were found for LOTIR and LOTIP (Tables 4 and 5). Compared to having no tobacco dependent parents, having two parents with a tobacco use-related disorder was associated with a faster LOTIR (by nearly five months, $p = 0.07$). Compared to having no addicted parents, having two parents with an alcohol or other drug disorder was associated with a faster LOTIP (over five months faster, $p = 0.09$). In future studies, these analyses might be improved using a measure of parents' times for transitions rather than their diagnostic status.

4.7. Individual differences of times for transitions

Variances in LOTIR, LOTIP, and LOTID were quite large and reduced the statistical power to detect significant differences. Moreover, at least some of the results observed herein may have been impacted by the skewed distributions of times for transitions (cf. Table 1 means and medians). Although the rank orders of means and medians were nearly always consistent, future analyses of times for transitions ought to explore techniques for gauging addictive liabilities

of substances based on median values. Past attempts to focus on individuals have relied on data analytic techniques such as configural frequency analysis or survival curve analysis (e.g., Ridenour et al., 2003,2005;Wagner & Anthony, 2002). Alternatives might be to examine median values of times for transitions or the proportion of users with 0.00 months between initiation and a transition (Table 1).

4.8. Limitations

Results of this study should be considered in light of the study limitations. Data were right censored, meaning that participants' data have only been collected as far as they have aged. Participants later could experience regular use, a DSM-III-R substance use-related criterion, or dependence. The study from which these data came will be continuing by following participants into adulthood; these analyses ought to be repeated when all of the participants have been followed up through the end of the currently planned last wave of data collection, age 28. Few participants initiated use of cocaine or opiates. More participants will initiate use of cocaine and opiates with later follow-ups of participants. It also is expected that greater numbers of participants will experience dependence through early adulthood.

Another related shortcoming of these analyses is that some individuals' data were used in multiple analyses. Hence, the results for LOTIR were not entirely independent of the results for LOTIP or LOTID. Although the present study provides a sufficient first examination of these phenotypes, future studies ought to further examine the different phenotypes using samples that are independent from the present sample. Longitudinal statistical techniques that account for repeated measures also could be useful for obtaining results for the different phenotypes.

Tobacco results should be considered preliminary, especially regarding comparisons with other substances, because the Fagerstrom measures were used in place of DSM abuse criteria. The generalizability of results should be tested in future studies, although several findings in this study were consistent with past studies which utilized dissimilar samples (Ridenour et al., 2003,2005;Wagner & Anthony, 2002). The advantages of this sample were critical to this line of research and are unique compared to existing samples. The study was longitudinal, included children with heterogeneous levels of risk for substance addiction, included rich data regarding participants' and parents' histories of substance involvement, and included sufficient numbers of females to test for gender differences. An important variable to consider in addictive liability research is availability—if a substance is not available to an individual, that individual's addictive liability will have no impact on his or her experience of addiction to the substance. One impact that drug availability might have had on these results is with regard to tobacco, which has become increasingly regulated in recent years in terms of sales to minors and legal penalties enforced for providing tobacco to minors.

4.9. Future directions

In addition to addressing the study limitations, the results suggest follow-ups to clarify and extend these findings. To clarify how genotypes might contribute to addictive liability, future studies are needed to learn which genotypes are associated with LOTIR, LOTIP, and LOTID and to clarify the mechanisms by which genotypes might impact addictive liability. One intermediary step toward studying associations between genotypes and addictive liability might be family, twin, or adoption studies in which LOTIR, LOTIP, or LOTID are measured in all family members. Another important area to clarify is the association(s) between psychiatric disorders and addictive liability in general, and LOTIR, LOTIP and LOTID specifically. Fortunately, the database from which the present data were drawn offers additional data to address each of these future steps to clarify the etiology of LOTIR, LOTIP, and LOTID.

4.10. Conclusions

This study expanded existing research on lengths of times for transitions as gauges of the addictive liabilities of substances. Results for LOTIR, LOTIP, and LOTID were consistent and suggest that the greatest addictive liability occurs with opiates, followed respectively, by cocaine, cannabis, tobacco and alcohol. Further research is needed to clarify what characteristics of substances generate different addictive liabilities as well as the mechanisms of substance consumption that lead to faster progressions. Females had slightly faster times to progression (suggesting greater addictive liabilities) compared to males, although this may not be true for the regular use transition. The results also suggest that familiarity may play a small role in addictive liability, above and beyond what is accounted for by differences between substances. Little of the differences between substances in times for progressions was accounted for by personal characteristics (Ridenour et al., 2005). It appears that specification of why substances differ in addictive liabilities in people could provide great insight regarding progression toward the last substance transition, addiction.

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References

- Agrawal A, Neale MC, Jacobson KC, Prescott CA, Kendler KS. Illicit drug use and abuse/dependence: Modeling of two-stage variables using the CCC approach. *Addictive Behaviors* 2005;30:1043–1048. [PubMed: 15893102]
- Agrawal A, Neale MC, Prescott CA, Kendler KS. A twin study of early cannabis use and subsequent use and abuse/dependence of other illicit drugs. *Psychological Medicine* 2004;34:1227–1237. [PubMed: 15697049]
- Ahmed SH, Koob GF. Transition from moderate to excessive drug intake: Change in hedonic set point. *Science* 1998;282:298–300. [PubMed: 9765157]
- American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 3th ed.. American Psychiatric Association; Washington, D.C.: 1987. DSM III-R
- American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed.. American Psychiatric Association; Washington, D.C.: 1994. DSM-IV
- Anthony JC, Warner LA, Kessler RC. Comparative epidemiology of dependence on tobacco, alcohol, controlled substances, and inhalants: Basic findings from the National Comorbidity Survey. *Experimental and Clinical Psychopharmacology* 1994;2:244–268.
- Ator NA, Griffiths RR. Principles of drug abuse liability assessment in laboratory animals. *Drug and Alcohol Dependence* 2003;70:S55–S72. [PubMed: 12759197]
- Bailey SL, Martin CS, Lynch KG, Pollock NK. Reliability and concurrent validity of DSM-IV subclinical symptom ratings for alcohol use disorders among adolescents. *Alcoholism, Clinical and Experimental Research* 2000;24:1795–1802.
- Balster RL, Bigelow GE. Guidelines and methodological reviews concerning drug abuse liability assessment. *Drug and Alcohol Dependence* 2003;70:S13–S40. [PubMed: 12759195]
- Bierut LJ, Dinwiddie SH, Begleiter H, Crowe RR, Hesselbrock V, Nurnberger JI, et al. Familial transmission of substance dependence: Alcohol, marijuana, cocaine, and habitual smoking. *Archives of General Psychiatry* 1998;55:982–988. [PubMed: 9819066]
- Boehm SL, Ponomarev I, Jennings AW, Whiting PJ, Rosahl TW, Garrett EM, et al. Gamma-Aminobutyric acid A receptor subunit mutant mice: New perspectives on alcohol actions. *Biochemical Pharmacology* 2004;68:1581–1602. [PubMed: 15451402]
- Brebner K, Froestl W, Andrews M, Phelan R, Roberts DCS. The GABA_B agonist CGP 44532 decreases cocaine self-administration in rats: Demonstration using a progressive ratio and a discrete trials procedure. *Neuropharmacology* 1999;38:1797–1804. [PubMed: 10587095]

- Breslau N, Johnson EO, Hiripi E, Kessler R. Nicotine dependence in the United States. *Archives of General Psychiatry* 2001;38:810–816. [PubMed: 11545662]
- Canagasaby A, Vinson DC. Screening for hazardous or harmful drinking using one or two quantity-frequency questions. *Alcohol and Alcoholism* 2005;40:208–213. [PubMed: 15797883]
- Carroll ME, France CP, Meisch RA. Food deprivation increases oral and intravenous drug intake in rats. *Science* 1979;205:319–321. [PubMed: 36665]
- Chen CY, Anthony JC. Epidemiological estimates of risk in the process of becoming dependent upon cocaine: Cocaine hydrochloride powder versus crack cocaine. *Psychopharmacology* 2004;172:78–86. [PubMed: 14598014]
- Chen K, Kandel DB, Davies M. Relationships between frequency and quantity of marijuana use and last year proxy dependence among adolescents and adults in the United States. *Drug and Alcohol Dependence* 1997;46:53–67. [PubMed: 9246553]
- Clark DB, Cornelius JR, Kirisci L, Tarter RE. Childhood risk categories for adolescent substance involvement: A general liability typology. *Drug and Alcohol Dependence* 2005;77:13–21. [PubMed: 15607837]
- Clark DB, Kirisci L, Moss HB. Early adolescent gateway drug use in sons of fathers with substance use disorders. *Addictive Behaviors* 1998;23:561–566. [PubMed: 9698986]
- Clark DB, Moss HB, Kirisci L, Mezzich AC, Miles R, Ott P. Psychopathology in preadolescent sons of substance abusers. *Journal of the American Academy of Child and Adolescent Psychiatry* 1997;36:495–502. [PubMed: 9100424]
- Clark DB, Pollock NA, Mezzich A, Cornelius J, Martin C. Diachronic assessment and the emergence of substance use disorders. *Journal of Child and Adolescent Substance Abuse* 2001;10:13–22.
- Cohen J. Things I have learned (so far). *American Psychologist* 1990;45:1304–1312.
- Cohen J. The earth is round (p b .05). *American Psychologist* 1994;49:997–1003.
- Cook TA, Luczack SE, Shea SH, Ehlers CL, Carr LG, Wall TL. Associations of ALDH2 and ADH1B genotypes with response to alcohol in Asian Americans. *Journal of Studies on Alcohol* 2005;66:196–204. [PubMed: 15957670]
- Dani JA, Ji D, Zhou RM. Synaptic plasticity and nicotine addiction. *Neuron* 2001;31:349–352. [PubMed: 11516393]
- Deroche-Gamonet V, Belin D, Piazza PV. Evidence for addiction-like behavior in the rat. *Science* 2004;305:1014–1017. [PubMed: 15310906]
- Dohrenwend BP, Levav I, Shrout PE, Schwartz S, Naveh G, Link BG, et al. Socioeconomic status and psychiatric disorders: The causation-selection issue. *Science* 1992;255:946–952. [PubMed: 1546291]
- Ellenbroek BA, van der Kam EL, van der Elst MCJ, Cools AR. Individual differences in drug dependence in rats: The role of genetic factors and life events. *European Journal of Pharmacology* 2005;255:946–952.
- Erdtmann-Vourliotis M, Mayer P, Riechert U, Voker Holtt V. Acute injection of drugs with low addictive potential (Δ^9 -tetrahydrocannabinol, 3,4-methylenedioxymethamphetamine, lysergic acid diamide) causes a much higher c-fos expression in limbic brain areas than highly addicting drugs (cocaine and morphine). *Molecular Brain Research* 1999;71:313–324. [PubMed: 10521585]
- Fernandez-Vidal JM, Spear NE, Molina JC. Adolescent rats discriminate a mild state of ethanol intoxication likely to act as an appetitive unconditioned stimulus. *Alcohol* 2003;30:45–60. [PubMed: 12878274]
- Fischman MW, Foltin RW. Utility of subjective-effects measurements in assessing abuse liability of drugs in humans. *British Journal of Addiction* 1991;86:1563–1570. [PubMed: 1786488]
- Griffiths RR, Bigelow GE, Ator NA. Principles of initial experimental drug abuse liability assessment in humans. *Drug and Alcohol Dependence* 2003;70:S41–S54. [PubMed: 12759196]
- Hasin D, Grant BF. The co-occurrence of DSM-IV alcohol abuse in DSM-IV alcohol dependence. *Archives of General Psychiatry* 2004;61:891–896. [PubMed: 15351767]
- Hasin D, Paykin A. Dependence symptoms but no diagnosis: Diagnostic “orphans” in a 1992 national sample. *Drug and Alcohol Dependence* 1999;53:215–222. [PubMed: 10080047]

- Hasin D, Van Rossem R, McCloud S, Endicott J. Differentiating DSM-IV alcohol dependence and abuse by course: Community heavy drinkers. *Journal of Substance Abuse* 1997;9:127–135. [PubMed: 9494944]
- Heatherton TF, Kozlowski LT, Frecker RC, Fagerstrom KO. The Fagerstrom test for nicotine dependence: A revision of the Fagerstrom tolerance questionnaire. *British Journal of Addiction* 1991;86:1119–1127. [PubMed: 1932883]
- Hill KG, White HR, Chung JJ, Hawkins JD, Catalano RF. Early adult outcomes of adolescent binge drinking: Person- and variable-centered analyses of binge drinking trajectories. *Alcoholism, Clinical and Experimental Research* 2000;24:892–901.
- Hollingshead, AB. Four Factor Index of Social Status. Yale University Department of Sociology; New Haven, CT7: 1990.
- Iacono WG, Carlson SR, Taylor J, Elkins JJ, McGue M. Behavioral disinhibition and the development of substance-use disorders: Findings from the Minnesota Twin Family Study. *Development and Psychopathology* 1999;11:869–900. [PubMed: 10624730]
- Jones HE, Johnson RE, Fudala PJ, Henningfield JE, Heishman SJ. Nalmefene: Blockade of intravenous morphine challenge effects in opioids abusing humans. *Drug and Alcohol Dependence* 2000;60:29–37. [PubMed: 10821987]
- Kandel D, Chen K, Warner LA, Kessler RC, Grant B. Prevalence and demographic correlates of symptoms of last year dependence on alcohol, nicotine, marijuana, and cocaine in the U.S. population. *Drug and Alcohol Dependence* 1997;44:11–29. [PubMed: 9031816]
- Kirisci L, Tarter RE, Vanyukov M, Reynolds M, Habeych M. Relation between cognitive distortions and neurobehavior disinhibition on the development of substance use during adolescence and substance use disorder by young adulthood: A prospective study. *Drug and Alcohol Dependence* 2004;76:125–133. [PubMed: 15488336]
- Koob GF, Le Moal M. Drug addiction, dysregulation of reward, and allostasis. *Neuropsychopharmacology* 2001;24:97–129. [PubMed: 11120394]
- Kreek MJ. Drug addictions: Molecular and cellular endpoints. *Annals of the New York Academy of Sciences* 2001;937:27–49. [PubMed: 11458539]
- Langenbucher JW, Labouvie E, Martin CS, Sanjuan PM, Bavly L, Kirisci L, et al. An application of item response theory analysis to alcohol, cannabis, and cocaine criteria in DSM-IV. *Journal of Abnormal Psychology* 2004;113:72–80. [PubMed: 14992659]
- Le Foll B, Sokoloff P, Stark H, Goldberg SR. Dopamine D3 receptor ligands block nicotine-induced conditioned place preferences through a mechanism that does not involve discriminative-stimulus or antidepressant-like effects. *Neuropsychopharmacology* 2005;30:720–730. [PubMed: 15562293]
- Martin CS, Pollock NK, Bukstein BG, Lynch KG. Inter-rater reliability of the SCID alcohol and substance use disorders section among adolescents. *Drug and Alcohol Dependence* 2000;59:173–176. [PubMed: 10891630]
- Merikangas KR, Stolar M, Stevens DE, Goulet J, Preisig MA, Fenton B, et al. Familial transmission of substance use disorders. *Archives of General Psychiatry* 1998;55:973–979. [PubMed: 9819065]
- Mulligan CJ, Robin RW, Osier MV, Sambuughin N, Goldfarb LG, Kittles RA, et al. Allelic variation at alcohol metabolism genes (ADH1B, ADH1C, ALDH2) and alcohol dependence in an American Indian population. *Human Genetics* 2003;113:325–336. [PubMed: 12884000]
- Nestler EJ. Historical review: Molecular and cellular mechanisms of opiate and cocaine addiction. *Trends in Pharmacological Sciences* 2004;25:210–218. [PubMed: 15063085]
- Nurnberger Jr, Wiegand R, Bucholz K, O'Connor S, Meyer ET, Reich T, et al. A family study of alcohol dependence: Coaggregation of multiple disorders in relatives of alcohol-dependent probands. *Archives of General Psychiatry* 2004;61:1246–1256. [PubMed: 15583116]
- Oslin DW, Berrettini W, Kranzler HR, Pettinati H, Gelernter J, Volpicelli JR, et al. A functional polymorphism of the A-opioid receptor gene is associated with naltrexone response in alcohol-dependent patients. *Neuropsychopharmacology* 2003;28:1546–1552. [PubMed: 12813472]
- Philpot RM, Badanich KA, Kirstein CL. Place conditioning: Age-related changes in the rewarding and aversive effects of alcohol. *Alcohol, Clinical and Experimental Research* 2003;27:593–599.

- Pollock NK, Martin CS. Diagnostic orphans: Adolescents with alcohol symptoms who do not qualify for DSM-IV abuse or dependence diagnoses. *American Journal of Psychiatry* 1999;156:897–901. [PubMed: 10360129]
- Ridenour TA, Cottler LB, Compton WM, Spitznagel EL, Cunningham-Williams RM. Is there a progression from abuse disorders to dependence disorders. *Addiction* 2003;98:635–644. [PubMed: 12751981]
- Ridenour TA, Maldonado-Molina M, Compton WM, Spitznagel EL, Cottler LB. Factors associated with the transition from abuse to dependence among substance abusers: Implications for a measure of addictive liability. *Drug and Alcohol Dependence* 2005;80:1–14. [PubMed: 16157227]
- SAS Institute Inc. SAS Proprietary Software Release 8.2 (for Windows). SAS Institute Inc; Cary, NC: 2001.
- Sarr M, Bucholz KK, Phelps DL. Using cluster analysis of alcohol use disorders to investigate “diagnostic orphans”: Subjects with alcohol dependence symptoms but no diagnosis. *Drug and Alcohol Dependence* 2000;60:295–302. [PubMed: 11053764]
- Schmidt FL, Hunter J. Are there benefits from NHST? *American Psychologist* 2002;57:65–66. [PubMed: 11885304]
- Schuckit MA, Smith TL, Danko GP, Bucholz KK, Reich T, Bierut L. Five-year clinical course associated with DSM-IV alcohol abuse or dependence in a large group of men and women. *American Journal of Psychiatry* 2001;158:1084–1090. [PubMed: 11431230]
- Schulze D, Jones BT. The effects of alcohol cues and an alcohol priming does on a multi-factorial measure of subjective cue reactivity in social drinkers. *Psychopharmacology* 1999;145:452–454. [PubMed: 10460323]
- Smith BJ, Jones HE, Griffiths RR. Physiological, subjective and reinforcing effects of oral and intravenous cocaine in humans. *Psychopharmacology* 2001;156:435–444. [PubMed: 11498721]
- Spitzer, R.; Williams, B.; Gibbon, M. Structured Clinical Interview for DSM-III-R. New York State Psychiatric Institute, Biometrics Research; New York7: 1988.
- Stafford D, LeSage MG, Glowa JR. Progressive-ratio schedules of drug delivery in the analysis of drug self-administration: A review. *Psychopharmacology* 1998;139:169–184. [PubMed: 9784071]
- Stevens, J. Applied multivariate statistics for the social sciences. 2nd ed. Lawrence Erlbaum; Hillsdale, N.J.7: 1992.
- Tarter RE, Kirisci L. Validity of the Drug Use Screening Inventory for predicting DSM-III-R substance use disorder. *Journal of Child and Adolescent Substance Abuse* 2001;10:45–53.
- Tarter RE, Kirisci L, Mezzich A, Cornelius J, Pajer K, Vanyukov M, et al. Neurobehavior disinhibition in childhood predicts early age onset at substance disorder. *American Journal of Psychiatry* 2003;160:1078–1085. [PubMed: 12777265]
- Tarter R, Vanyukov M, Giancola P, Dawes M, Blackson T, Mezzich A, et al. Etiology of early age onset substance use disorder: A maturational perspective. *Development and Psychopathology* 1999;11:657–683. [PubMed: 10624720]
- Tsuang MT, Lyons MJ, Meyer JM, Doyle T, Eisen SA, Goldberg J, et al. Co-occurrence of abuse of different drugs in men: The role of drug-specific and shared vulnerabilities. *Archives of General Psychiatry* 1998;55:967–972. [PubMed: 9819064]
- U.S. Department of Health and Human Services. A report of the surgeon general: 1-10. U.S.D.H.H.S.; Atlanta:: 1994. Preventing tobacco use among young people.
- Vanderschuren LJMJ, Everitt BJ. Drug seeking becomes compulsive after prolonged cocaine self-administration. *Science* 2004;305:1017–1019. [PubMed: 15310907]
- Vanyukov MM, Tarter RE, Kirisci L, Kirillova GP, Maher BS, Clark DB. Liability to substance use disorders: 1. Common mechanisms and manifestations. *Neuroscience and Biobehavioral Reviews* 2003;27:507–515.
- Vastola BJ, Douglas LA. Nicotine-induced conditioned place preference in adolescent and adult rats. *Physiology and Behavior* 2002;77:107–114. [PubMed: 12213508]
- Volkow ND, Fowler JS, Wang GJ, Swanson JM. Dopamine in drug abuse and addiction: Results from imaging studies and treatment implications. *Molecular Psychiatry* 2004;9:557–569. [PubMed: 15098002]

- Wagner FA, Anthony JC. From first drug use to drug dependence: Developmental periods of risk for dependence upon marijuana, cocaine, and alcohol. *Neuropsychopharmacology* 2002;26:479–488. [PubMed: 11927172]
- Winger, G.; Young, AM.; Woods, JH. Ethanol as a reinforcer: Comparison with other drugs. In: Kissin, B.; Begleiter, H., editors. *The pathogenesis of alcoholism: Biological factors*. Plenum Press; New York.: 1983. p. 107-131.

Fig. 1. Months from first use to regular use (LOTIR) for alcohol, tobacco, or cannabis users. *Note:* Legend: (____) survival curve in months for alcohol regular use; (____) survival curve in months for tobacco regular use; (.....) survival curve in months for cannabis regular use.

Fig. 2. Months from first use to first substance use problem (LOTIP) for alcohol, tobacco, or cannabis users *Note:* Legend: (____) survival curve in months for alcohol problem; (_ _ _) survival curve in months for tobacco problem; (.....) survival curve in months for cannabis problem.

Fig. 3.

Months from first use to first dependence (LOTID) for alcohol, tobacco, or cannabis users.

Note: Legend: (____) survival curve in months for alcohol dependence; (____) survival curve in months for tobacco dependence; (.....) survival curve in months for cannabis dependence.

Table 1

Sample sizes of lifetime users, proportions of lifetime users, and ages of users at different stages of substance involvement

	Initiation "n": age onset in years	Regular use "n": mo after initiation	First problem "n": mo after initiation	Dependence "n": mo after initiation
Tobacco	<i>n</i> =315 (14.48, 3.10) Median=14.50	249; 79.05% (9.59, 23.78) Median=0.00	90; 28.57% (22.40, 26.45) Median=12.00	27; 8.45% (31.11, 33.66) Median=12.00
Alcohol	<i>n</i> =426 (14.57, 2.64) Median=15.00	340; 79.81% (18.69, 28.76) Median=0.00	197; 46.24% (28.42, 28.35) Median=24.00	65; 15.25% (38.44, 27.95) Median=36.00
Cannabis	<i>n</i> =320 (15.72, 1.96) Median=15.50	221; 66.06% (4.72, 9.67) Median=0.00	159; 49.69% (13.21, 18.17) Median=0.00	52; 16.25% (28.62, 27.32) Median=24.00
Cocaine	<i>n</i> =33 (18.89, 2.16) Median=18.50	18; 54.55% (2.67, 8.79) Median=0.00	17; 51.52% (3.53, 9.26) Median=0.00	8; 24.24% (4.50, 12.73) Median=0.00
Opiates	<i>n</i> =38 (18.05, 1.86) Median=18.00	21; 55.26% (1.71, 7.86) Median=0.00	16; 40.00% (1.50, 4.10) Median=0.00	8; 21.05% (1.50, 4.24) Median=0.00

Note: Problem onset was the age at which the first DSM-III-R abuse or dependence criterion was experienced (or first *Fagerstrom* item was experienced for tobacco). Start of dependence onset was the age at which DSM-III-R dependence criteria were experienced for at least one month. Percentages are the prevalence of lifetime users of a substance that progressed to the stage of substance involvement specified for the column. Parenthetical values are: mean, standard deviation. mo = month.

Table 2

Gender differences on lengths of times for transitions for alcohol, tobacco, and cannabis

	Transition from initiation	Gender	n	Mean length of time in mo	Median	p-value
Tobacco	Regular use	Males	203	9.93 (24.83)	0.00	0.6358
		Females	46	8.09 (18.60)	0.00	
	First problem	Males	76	24.47 (27.74)	12.00	0.0831
		Females	14	11.14 (13.69)	6.00	
	Dependence	Males	27	31.11 (33.66)	0.00	na
		Females	0	na	na	
Alcohol	Regular use	Males	276	19.39 (30.68)	0.00	0.3566
		Females	64	15.70 (18.18)	12.00	
	First problem	Males	164	30.15 (29.31)	22.00	0.0567
		Females	33	19.85 (21.31)	22.00	
	Dependence	Males	58	38.86 (28.18)	36.00	0.7328
		Females	7	35.00 (27.77)	24.00	
Cannabis	Regular use	Males	177	4.27 (9.43)	0.00	0.1630
		Females	44	6.55 (10.50)	0.00	
	First problem	Males	135	13.78 (18.22)	12.00	0.3497
		Females	24	10.00 (17.93)	0.00	
	Dependence	Males	50	28.32 (27.40)	24.00	na
		Females	2	36.00 (33.94)	36.99	

Note: Problem onset was the age at which the first DSM-III-R abuse or dependence criterion was experienced (or first *Fagerstrom* item was experienced for tobacco). Start of dependence onset was the age at which DSM-III-R dependence criteria were experienced for at least one month. Parenthetical values are standard deviations.

Table 3

Associations between outcome diagnostic status and lengths of times for transitions for alcohol, tobacco, and cannabis, controlling for age of use onset

	Transition from initiation	Experienced dependence	n	Mean length of time in mo	Median	P-value
Tobacco	Regular use	Yes	27	9.33 (19.50)	0.00	0.72
		No	222	9.62 (24.29)	0.00	
	First problem	Yes	26	21.23 (27.43)	12.00	0.44
		No	64	22.88 (26.25)	12.00	
Alcohol	Regular use	Yes	64	15.80 (23.16)	0.00	0.06
		No	276	19.37 (29.91)	0.00	
	First problem	Yes	65	27.55 (24.39)	24.00	0.87
		No	132	28.85 (30.18)	24.00	
Cannabis	Regular use	Yes	50	3.12 (6.78)	0.00	0.16
		No	171	5.19 (10.33)	0.00	
	First problem	Yes	15	16.47 (19.19)	12.00	0.26
		No	108	11.67 (17.55)	0.00	

Note: Problem onset was the age at which the first DSM-III-R abuse or dependence criterion was experienced. Dependence was based on having experienced DSM-III-R dependence related to the drug specified in the row (or not). Parenthetical values are standard deviations.

Table 4

Can differences between drugs in length of time for progression to regular use (LOTIR) be accounted for by gender or number of parents with substance use disorders?

Regression model	Predictor	Beta weight	'p' for unique variance
Drug type only ($R^2=0.07$; $R=0.26$; $p<0.0001$)	Tobacco	-9.10	<0.01
	Cannabis	-13.97	<0.01
	Cocaine	-16.03	<0.01
	Opiates	-16.98	<0.01
Drug type plus gender/parents ($R^2=0.07$; $R=0.27$; $p<0.0001$)	Tobacco	-9.05	<0.01
	Cannabis	-13.45	<0.01
	Cocaine	-15.58	<0.01
	Opiates	-16.17	<0.01
	Gender (Female = 1)	-2.16	=0.23
	1 Parent with SUD	1.75	=0.50
	2 Parents with SUD	0.84	=0.73
	1 Parent with TUD	-3.09	=0.26
	2 Parents with TUD	-4.73	=0.07

Note: Referent group for drugs was alcohol. Referent group for parent substance use variables was having zero parents with SUD or TUD. Beta weights are unstandardized and indicate the mean number of months in time for transition associated with the predictor, compared to male users of alcohol with no parents having an SUD or TUD. SUD = any DSM-III-R abuse or dependence disorder excluding tobacco. TUD = tobacco use disorder (as measured by a score of 1 or greater on the *Fagerstrom Test for Nicotine Dependence*).

Table 5

Can differences between drugs in length of time for progression to first problem (LOTIP) be accounted for by gender or number of parents with substance use disorders?

Regression model	Predictor	Beta weight	'p' for unique variance
Drug type only ($R^2=0.10$; $R=0.32$; $p<0.01$)	Tobacco	-6.02	=0.05
	Cannabis	-15.21	<0.01
	Cocaine	-24.89	<0.01
	Opiates	-29.92	<0.01
Drug type plus gender/parents ($R^2=0.12$; $R=0.35$; $p<0.01$)	Tobacco	-4.81	=0.13
	Cannabis	-14.67	<0.01
	Cocaine	-24.40	<0.01
	Opiates	-26.62	<0.01
	Gender (Female = 1)	-7.84	<0.01
	1 Parent with SUD	-2.61	=0.44
	2 Parents with SUD	-5.30	=0.09
	1 Parent with TUD	0.86	=0.80
	2 Parents with TUD	2.66	=0.41

Note: Referent group for drugs was alcohol. Referent group for parent substance use variables was having zero parents with SUD or TUD. Beta weights are unstandardized and indicate the mean number of months in time for transition associated with the predictor, compared to male users of alcohol with no parents having an SUD or TUD. SUD = any DSM-III-R abuse or dependence disorder excluding tobacco. TUD = tobacco use disorder (as measured by a score of 1 or greater on the *Fagerstrom Test for Nicotine Dependence*).

Table 6

Can differences between drugs in length of time for progression to dependence (LOTID) be accounted for by gender or number of parents with substance use disorders?

Regression model	Predictor	Beta weight	dpT for unique variance
Drug type only ($R^2=0.12$; $R=0.35$; $p<0.01$)	Tobacco	-7.34	=0.25
	Cannabis	-9.83	=0.05
	Cocaine	-33.95	<0.01
	Opiates	-36.95	<0.01
Drug type plus gender/parents ($R^2=0.14$; $R=0.37$; $p=0.02$)	Tobacco	-3.49	=0.61
	Cannabis	-10.52	=0.07
	Cocaine	-34.15	<0.01
	Opiates	-39.25	<0.01
	Gender (Female = 1)	-2.04	=0.82
	1 Parent with SUD	-0.29	=0.97
	2 Parents with SUD	2.23	=0.73
	1 Parent with TUD	-6.87	=0.34
	2 Parents with TUD	1.09	=0.87

Note: Referent group for drugs was alcohol. Referent group for parent substance use variables was having zero parents with SUD or TUD. Beta weights are unstandardized and indicate the mean number of months in time for transition associated with the predictor, compared to male users of alcohol with no parents having an SUD or TUD. SUD = any DSM-III-R abuse or dependence disorder excluding tobacco. TUD = tobacco use disorder (as measured by a score of 1 or greater on the *Fagerstrom Test for Nicotine Dependence*).