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The differential impact of risk factors on illicit drug involvement in females

■ **Abstract** *Background* Initiation of drug use and progression to abuse/dependence involve complex pathways. Potential risk factors may correlate with initiation or progression or both. Are there risk factors that associate with illicit drug use or illicit drug abuse/dependence? Is the magnitude of the association the same for use and abuse/dependence? Does this pattern of association differ across categories of drugs? *Methods* We used data from female-female adult twins to assess the association of 26 putative risk factors with use and abuse/dependence of six illicit psychoactive drugs. Drug involvement was represented by independent dichotomous outcomes and by a single ordinal variable. Odds ratios were obtained by logistic regression and a continuation ratio was used to test the magnitude of association. *Results* Factors associate in similar patterns with different drug categories. Some associated factors interact only with initiation while others relate with both stages. There is a stronger association of significant socio-demographic factors with drug use while the psychiatric diagnoses are more strongly associated with progression to abuse/dependence. *Conclusions* Risk factors may be use-specific, abuse/dependence-specific or common to use and abuse/dependence. The trend of associations is similar across different illicit drugs. This suggests complex, interacting pathways that determine drug habits in individuals. These results are hypothesis-generating and future studies of causal relationships may draw from the outcomes presented in these analyses.

■ **Key words** illicit drugs – use – abuse/dependence – risk factors – continuation ratio

Introduction

The procurement, use and misuse of psychoactive substances is a source of significant public health concern. The primary challenges in the epidemiological study of drug involvement arise from two important characteristics of the process. Firstly, drug involvement is a multistage process with a proximal initiation or use stage, which is marked by recreational or experimental use of a psychoactive substance, and a distal abuse and dependence stage, which is distinguished by symptoms of tolerance and/or withdrawal. An individual's drug habit, therefore, represents a complex, multistage process. Drug use is distinct, physiologically, pharmacologically and behaviorally from subsequent abuse or dependence. Additionally, the pathway to abuse/dependence is contingent on initiation. In other words, potential to abuse/dependence cannot be measured in individuals who have never initiated use of the psychoactive substance. While in this manuscript we are interested in the proximal and distal stages of drug involvement (use and abuse/dependence), it is important to note that drug users may traverse a variety of pathways (e. g., use to heavy use to abuse/dependence or use to abuse/dependence, directly) in order to progress along the pathway of addiction. Furthermore, all users of psychoactive drugs do not proceed to abuse/dependence and this heterogeneity provides an additional layer of complexity to the study of drug involvement.

The second challenge posed to the analysis of drug

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involvement is the complex inter-relationships between stages of drug involvement and risk factors that associate with one or more of these stages. For instance, epidemiological studies propose a strong association between impulse-disinhibition, novelty-seeking and illicit drug involvement, especially marijuana, cocaine and ecstasy use (Laviola et al. 1999; Dughiero et al. 2001; Eisenman et al. 1980). In contrast, results from large-scale epidemiological studies, such as the International Congress for Psychiatric Epidemiology (ICPE), and data from the Epidemiological Catchment Area (ECA) have shown a strong association between Axis I psychiatric diagnoses and illicit drug abuse/dependence (Merikangas et al. 1998; Regier et al. 1990). Most notably, in the ICPE study, using data from the National Comorbidity Survey and data from other international sites, Merikangas and colleagues showed that the association between psychiatric illness, such as affective, anxiety and conduct disorders, and drug abuse/dependence (OR = 3.3–15.2) was much stronger than the association between psychiatric illness and drug use (OR = 1.8–4.9) (Merikangas et al. 1998). Other risk factors, such as measures of religiosity, tend to have a protective influence on drug use and abuse/dependence (Clark and Midanik 1982; Rachal et al. 1976; Gorsuch and Butler 1976a). These trends of association suggest that risk factors associating with drug involvement may be classified in the following manner: risk factors that are uniquely correlated with drug use, risk factors that are uniquely associated with drug abuse/dependence and risk factors that correlate with use and abuse/dependence, but the magnitude of the association may differ for each stage. While a brief overview of the literature for each class of risk factors is presented, it is important to note that the data for this manuscript come from non-overlapping interviews where drug involvement and putative risk factors were measured at different waves of interviews and each variable was assessed only once. Hence, while the term "risk factor" is used to denote the measures that may bear some relationship with drug involvement, this manuscript only attempts to examine correlations and not causal pathways.

This study had the following goals: (1) to examine the extent of association between six categories of illicit drugs, including a composite category of "any illicit drug", and 26 putative risk factors, individually for illicit drug use and abuse/dependence. Odds ratios (ORs) were used to measure the association between the dichotomous drug variable and the risk factors; and (2) to examine the magnitude of the association between 26 putative risk factors and drug involvement, when drug involvement is considered to be a multistage process with two important transitions (abstinence to use and use to abuse/dependence). The continuation ratio (CR) (an adapted odds ratio) was employed to measure the association between the ordinal three-level drug variable (0 = abstinence, 1 = use, 2 = abuse/dependence) and the risk factors (MacLean 1988).

The risk factors used in this study were selected based on prior evidence for their role in illicit drug involvement. These 26 risk factors may be classified under the following sub-headings:

(1) Socio-demographic factors, such as income and history of divorce
(2) Religiosity measures, such as personal devotion
(3) Personality measures, such as novelty-seeking, extraversion and neuroticism
(4) Childhood risk factors, such as childhood sexual abuse
(5) Psychiatric illness, such as major depression and generalized anxiety disorders.

Socio-demographic factors, like income, have been extensively studied in the formulation of the social selection vs. causation hypothesis (Dohrenwend 2000; Johnson et al. 1999). Low income and loss of employment are correlated with illicit drug involvement. Other factors, such as marital dissolution and divorce are positively correlated with drug involvement (Davis and DiNitto 1996; Horwitz et al. 1996; Power et al. 1999). In a study of 672 middle-aged adults, Schwarz and colleagues showed a positive correlation between marital conflict and alcohol consumption (Schwarz and Wheeler 1992). Non-traditional cohabitation is also associated with drug involvement, according to Lye and Waldron (1998).

Measures of religiosity are strongly associated with drug involvement, especially for illicit drugs, and are proposed to have a protective influence. In a study using a sub-sample of the data used in this manuscript, Kendler et al. showed that high levels of personal devotion may be negatively associated with substance use disorders (Kendler et al. 2003). In a study of African-American adolescents, Wills and colleagues also noted an inverse association between religiosity and substance use (Wills et al. 2003).

In contrast to the proposed "buffering" effect of high levels of religiosity (Wills et al. 2003), high scores on certain personality measures, like neuroticism, extraversion and novelty-seeking are positively correlated with illicit drug involvement. Several cross-sectional and clinical studies have noted a robust association between novelty-seeking and illicit drug use (Laviola et al. 1999; Lynskey et al. 1998; Dughiero et al. 2001). High levels of novelty-seeking and neuroticism were associated with increased 3-4 methylenedioxymethamphetamine (MDMA) use in males enrolled for compulsory military service (Bobes et al. 2002). High extraversion scores are also positively correlated with frequent illicit drug use (Spotts and Shontz 1984, 1991). While novelty-seeking, neuroticism and extraversion are the most commonly examined personality traits, this study also includes measures of personality, such as self-esteem and locus-of-control, which have been proposed to play a role in the development of the drug habit (Siewert et al. 2003).

Two measures, childhood sexual abuse (CSA) and parental warmth, that reflect childhood influences were included as putative risk factors. Childhood sexual

abuse is positively correlated with drug involvement (Simpson and Miller 2002; Freeman et al. 2002; Teusch 2001; MacMillan et al. 1997; Nelson et al. 2002). Simpson and Miller, in a review, note a strong positive correlation between incidence of CSA and substance use problems in adolescence and adulthood (Simpson and Miller 2002). In contrast, a high level of parental warmth and parental care is negatively associated with the incidence of substance use problems (Gerra et al. 2004). A study by Hawkins and colleagues showed an inverse association between maternal bonding and tobacco misuse in adolescents (Hawkins et al. 1992).

One of the most important categories of putative risk factors associated with drug involvement is psychiatric illness, such as depression and anxiety. Our study includes six Axis I psychiatric diagnoses: major depression (MD), generalized anxiety disorder (GAD), conduct disorder (CD), panic disorder, phobic disorder and bulimia nervosa (BN). Numerous studies have proposed a positive correlation between psychiatric illness and illicit drug involvement, especially abuse/dependence (Luthar et al. 1992; Rounsaville et al. 1991; Merikangas and Avenevoli 2000; Merikangas et al. 1998; Kandel et al. 1997, 1999; Kendler and Gardner Jr 1998). Kandel and colleagues noted an elevated likelihood of psychiatric illness in 9- to 18-year-olds reporting illicit substance use (Kandel et al. 1997). Degenhardt and colleagues showed that cannabis and tobacco use were positively associated with mental illness in their sample of Australian adults (Degenhardt et al. 2001).

The current body of literature posits a substantial association between risk factors and illicit drug involvement. While the odds ratios between the risk factors and substance use disorders shed considerable light on the process of development of the drug habit, they do not partition the risk factors into stage-specific risk factors and risk factors common to illicit drug use and abuse/dependence. We were interested in establishing a categorization of risk factors (use-specific, abuse/dependence-specific and common). Furthermore, we also extend our analyses from using an OR to using an adapted CR, which examines whether the magnitude of the association between a risk factor and a specific stage in drug involvement is identical or different for multiple stages (MacLean 1988; Heagerty and Zeger 2000; Dos Santos and Berridge 2000). We would expect, therefore, that, even within the category of risk factors common to illicit drug use and abuse/dependence, there would be certain risk factors that would associate more strongly with the initiation stage or the progression stage. Overall, the OR and CR will provide a pattern of risk factors that correlate, positively or negatively, with different stages of illicit drug involvement. Furthermore, by studying multiple classes of illicit drugs, we may examine whether this trend of associations is similar or different for different classes of illicit drugs.

Subjects and methods

Subjects

The female same-sex twin data (N = 1943) used in this analysis are part of a longitudinal study of putative risk factors and illicit drug use, abuse and dependence. Female twins and triplets were ascertained from the population-based Virginia Twin Registry, now a part of the Mid-Atlantic Twin Registry (MATR) and were eligible to participate if they were Caucasian and were born between 1934 and 1974. Respondents who agreed to participate were interviewed in the first wave (FF1) of personal interviews. Zygosity was initially determined by standard questions and a sub-sample was later confirmed by Polymerase Chain Reaction (PCR) analyses (Kendler et al. 2000). Three follow-up interviews have been completed (FF2, FF3 and FF4, respectively). The drug use and abuse/dependence variables were only measured at the fourth wave, along with childhood sexual abuse and demographic measures. Data for the measures of religiosity and the psychiatric diagnoses were obtained from the third wave of interviews, while personality traits were measured from responses to a self-report questionnaire that comprised the first wave of interviews. It may be noted that, although four waves of data are available, these datasets are non-overlapping and do not include risk factors for drug involvement measured at multiple occasions. Each wave of interviews aimed to collect additional data and did not necessarily repeat measurements taken at a previous interview and, hence, while multiple waves of data are available, we currently do not have multiple occasions of measurement of variables to study causal pathways between risk factors and illicit drug involvement. Ascertainment details for data collection are available elsewhere (Kendler et al. 1997; Kendler et al. 2003). As approved by the institutional review board of Virginia Commonwealth University, prior to interviews, subjects were informed about the aims of the study and informed consent was obtained.

Measures

Drug use and abuse/dependence data

The FF4 section diagnosing drug use had the following drug categories: cannabis (e.g., hashish and marijuana), cocaine (e.g., intranasal, freebase and crack), and sedatives (e.g., Quaalude, seconal and Valium), stimulants (e.g., speed, ecstasy and Ritalin) and hallucinogens (e.g., LSD, mescaline and PCP). A composite category of "any illicit drug" was also created. "Any illicit drug" is a fairly heterogeneous category, with maximum power, which reflects use (and abuse/dependence) of either cannabis or cocaine or sedatives or stimulants or hallucinogens or opiates (which was not included independently due to poor prevalence of use and abuse/dependence). For all prescription drugs, illicit use was strictly defined as use of the drug (i) without a prescription, (ii) in greater amounts/more often than prescribed, or (iii) for use other than those prescribed.

In the questionnaire, lifetime use of an illicit drug was assessed through the participant's response to a questionnaire item regarding lifetime use of the aforementioned drugs. Abuse and dependence were diagnosed using an adaptation of the Structural Clinical Interview for DSM-III-R Diagnosis (SCID) (Spitzer et al. 1987). A combined abuse and/or dependence diagnosis was used to maximize power in our study. The number of individuals with abuse alone and dependence alone is fairly small for some of the illicit drugs and we collapsed the categories to ensure adequate sample sizes for analyses.

Drug involvement was coded in two different ways, depending on the method of analysis. For the calculation of odds ratios, drug use was coded as a dichotomous variable (0 = never used and 1 = used once or more in their lifetime). Similarly, abuse/dependence was also coded as a dichotomous outcome (0 = neither abuse nor dependence and 1 = abuse and/or dependence). For the calculation of continuation ratios, a single three-level ordinal variable was created to assess illicit drug involvement (0 = never used, 1 = use but not abuse/dependence and 2 = use and abuse and/or dependence).

Putative risk factors

The socio-demographic risk factors included age at the time of assessment (in years), years of education, family income (mid-point of reported range of income in USD), individual income (mid-point of reported range of income in USD), history of divorce (scored as 1 if ever divorced and 0 if not) and current cohabitation (married or living with someone or in an intimate relationship) (scored as 1 if currently cohabiting and 0 if not).

Three dimensions of religiosity were identified based on a scale developed by Kendler, by performing a factor analysis, details for which are available elsewhere (Kendler et al. 1997, 2003). Personal devotion refers to items assessing personal religious commitment and devotion (e. g., "How important are your religious and spiritual beliefs in your daily life?"). Personal conservatism refers to items reflecting a traditional or fundamentalist view of religion (e. g., "Do you believe that God or a universal spirit observes your actions and rewards or punishes you for them?"). Institutional conservatism refers to items assessing religious affiliation (e. g., fundamentalist Protestant, Baptist, Catholic, mainline Protestant or other Baptist).

The eight personality measures assessed were neuroticism (Eysenck et al. 1985), extraversion (Eysenck et al. 1985), altruism [defined by seven items from the Interpersonal Reactivity Index (Davis 1980) assessing sensitivity to the feelings of others], interpersonal dependency (Hirschfeld et al. 1977), mastery [reverse coding of the Powerlessness sub-scale of the Alienation test (Maddi et al. 1979)], optimism (Scheier and Carver 1985), self-esteem (Rosenberg 1965), locus-of-control [based on the learned resourcefulness sub-scale of the Attributional Style Questionnaire (Peterson et al. 1982)] and novelty-seeking [based on the Tridimensional Personality Questionnaire (Cloninger 1987)].

Parental warmth was measured using a modified version of the Parental Bonding Instrument (Parker 1990) and assessed the relationship between parent and child up until the age of 16 years (e. g., "…mother and father spoke to you with a warm and friendly voice"). Childhood sexual abuse was a binary variable based on self-reported incidence of sexual abuse before the age of 16, including touching or fondling or sexual intercourse with an older individual (Martin et al. 1993). Further details regarding these variables are available in a prior publication (Kendler et al. 2002).

Six Axis I psychiatric disorders were included in the study. Major depression was a lifetime measure coded as a binary variable (Kendler and Prescott 1999). GAD was also coded as a binary measure, but a 1-month rather than 6-month minimum duration of illness was used to maximize power. Lifetime phobia and panic disorder was based on a DSM diagnosis of a broad definition of panic disorder and was also dichotomous, as was bulimia nervosa. Phobia was diagnosed using an adaptation of DSM-III criteria and the DIS interview (Robins and Helzer 1985) which required the presence of one or more of the 22 fears which the respondent recognized as unreasonable and that, in the judgment of the interviewer, objectively interfered with the respondent's life. Full-length definitions of the anxiety disorders, the methods for their construction and prevalences are detailed elsewhere (Kendler et al. 2002). Assessment of conduct disorders inquired about three or more conduct disorder behaviors prior to the age of 15.

Statistical analyses

In order to deal with incomplete data due to a multiwave sample and to maximize power, we performed multiple imputations on the dataset using a beta version of IVEware (Raghunathan et al. 1999). IVEware generates imputed values for missing variables using a sequential, multiple regression technique. The regression technique is based on the type of variable being imputed. The imputations draw from the posterior predictive distribution of the missing variable assuming a non-informative prior distribution. The procedure is performed iteratively in order to exploit the covariance structure of the data assuming the variables are missing at random. One imputed dataset was used for all the analyses.

All measures except lifetime psychiatric diagnoses, current cohabitation, history of divorce, age and years of education were standardized. As a result of the standardization procedure, ORs reflect changes in association for every SD change in the independent variable.

The association between each risk factor and illicit drug involvement was assessed individually for drug use and abuse/dependence, using PROC LOGISTIC in SAS (SAS Institute 1999). Therefore, for each drug and each individual risk factor, we obtained two ORs (one for use and the risk factor and one for abuse/dependence and the risk factor). To account for clustering of data in logistic regression due to a twin sample, we repeated the analyses for cannabis and sedatives using independence estimating equations (IEE). This technique treats the correlational structure as independent and is robust to misspecification. PROC GENMOD was employed to obtain parameter estimates and standard errors (SE) (Liang and Zeger 1986). The SE varied marginally when IEE was used instead of logistic regression. However, this did not result in any change of parameter estimates for the two drug categories.

In the second stage of the analyses, we used the three-level ordinal variable to represent illicit drug involvement (0 = never use, 1 = use but no abuse/dependence and 2 = use and abuse and/or dependence) and examined the association between each risk factor and the single ordinal variable. Therefore, each analysis provided one CR (MacLean 1988). The interpretation of the CR has two key elements: statistical significance of the CR and the sign of the CR. A statistically significant CR suggests that the association of the independent variable (risk factor) with each of the dependent variables, i. e., either use or abuse/dependence, is significantly different. Therefore, a zero CR suggests that there is no difference in the manner in which the risk factor is correlated with drug use and drug abuse/dependence. Furthermore, the sign of the CR determines whether the association between the risk factor and the two transitions in drug involvement (abstinence to use and use to abuse/dependence) is stronger for the first or the second transition. A negative CR indicates that the risk factor is more strongly associated with use or initiation of drug involvement than with progression to abuse/dependence, while a positive CR suggests that the risk factor is more strongly associated with progression to abuse/dependence than with initiation. Schnurr et al. applied the CR method to a study of risk factors on the development and maintenance of posttraumatic stress disorder (PTSD) (Schnurr et al. 2004). An illustration of the CR method to substance use data may be found in a study by Kendler et al. where the two-stage relationship between putative risk factors and smoking initiation and nicotine dependence is assessed using the CR method (Kendler et al. 1999).

Results

■ Sample characteristics

At the time of the first interview, the mean age of the participants was 28.8 years (range 17–62 years) and the median age was 28.0 years. Mean level of education was 14.3 years (range 3–20 years) with a median of 14.0 years. Table 1 lists the number of individuals in each drug category for initiation and progression. Mean age of initiation and progression for all categories (except 'any drug') is also presented in Table 1.

Table 2 lists the putative risk factors that were statistically significant in our analyses. The risk factors are distributed as "use-specific", "abuse/dependence-specific" and "common". Also, for the risk factors common to use and abuse/dependence, the relative direction of the CR is noted. Table 3 lists the ORs for initiation, progression and CRs for all the 26 variables for each of the six drug categories. We review results for each of the five categories of risk factors. For each sub-heading of risk factors (socio-demographic, religiosity, personality

Table 1 Proportion of female twins (N = 1935) who initiated drug use and the percentage that progressed to abuse/dependence with the mean age

Drug	Use (N = 1943)	Use and abuse/dependence (% of users)	Mean age (years): use	Mean age (years): abuse/dependence
Illicit drugs				
Any drug	967	204 (21.1%)	–	–
Cannabis	925	146 (15.8%)	18.8	19.1
Cocaine	271	62 (22.9%)	22.1	24.6
Sedatives	147	33 (22.4%)	22.7	23.6
Stimulants	199	63 (31.7%)	19.7	21.4
Hallucinogens	201	17 (8.5%)	19.5	19.8

* Subtract value from N = 1943 for non-initiators/abstainers
** Subtract value from N = 1943 for initiation (ordinal level = 0) to get initiation without progression to abuse/dependence (ordinal level = 1). Ordinal level = 2 is initiation with progression to abuse/dependence

Table 2 Overview of statistically significant findings (OR and CR) for five categories of illicit drugs and a composite "any illicit drug" category

	Any illicit drug*	Cannabis	Cocaine	Sedatives	Stimulants	Hallucinogens
Use-specific risk factors	Age Income Divorce Religiosity Extraversion Neuroticism Altruism Novelty-seeking	Age Income Divorce Religiosity Extraversion Altruism Novelty-seeking CSA Parental warmth Phobia	Age Religiosity Extraversion Novelty-seeking	Age Divorce Novelty-seeking CSA GAD Panic disorder Phobia	Age Divorce Religiosity Novelty-seeking	Divorce Religiosity Altruism Parental warmth Panic disorder
Abuse/dependence-specific risk factors	Education Optimism GAD	Optimism GAD MD	Parental warmth Panic disorder		Mastery Self-esteem MD	CSA MD
Common to use and abuse/dependence	CSA[2] Parental warmth[1] Panic disorder[2] Phobia[2] MD[2]	Panic disorder[2]	Divorce[1] CSA[2] MD[2]	MD[2]	CSA[2] Panic disorder[2] GAD[2]	Novelty-seeking[2]

* Includes cannabis, cocaine, sedatives, stimulants, hallucinogens and opiates
Note: The risk factors listed in Table 2 refer to statistically significant risk factors from Table 3. The numerical superscript is provided only for the risk factors that were significantly associated with illicit drug use and abuse/dependence and refer to their CR. Superscript "1" refers to a negative CR and means that the risk factor associates more closely with drug initiation or use. Superscript "2" refers to a positive CR and means that the risk factor associates more closely with progression from use to abuse/dependence

measures, childhood risk factors and psychiatric illness), the individual association between drug use and abuse/dependence with the risk factors is discussed first, followed by a short description of the CR which measures the association between the risk factor and the ordinal variable for drug involvement.

■ Socio-demographic variables

Cohabitation was unrelated to the illicit drugs. In contrast, history of divorce was positively associated with illicit drug use for all illicit drugs (Table 3: OR = 1.71–2.56). Individual and family income was associated with use of cannabis and the composite category of any illicit drug. When drug involvement was treated as an ordinal (instead of dichotomous) variable, the CRs were consistently negative, suggesting that for

all socio-demographic risk factors, even when both individual ORs were not statistically significant, the relationship between the risk factor and illicit drug use was much stronger than the relationship between the risk factor and illicit drug abuse/dependence (Table 3).

■ Religiosity

We see from Table 2 that high levels of personal devotion, personal conservatism and institutional conservatism were associated with lowered likelihood of use of all illicit drugs except sedatives (Table 3: OR = 0.60–0.88). In contrast, these measures of religiosity were unrelated to illicit drug abuse/dependence. While the OR between religiosity and drug abuse/dependence was not statistically significant, the CR suggested that religiosity has a strong correlation with use

Table 3 Odds ratios (ORs) for use and abuse/dependence (A/D) of cannabis, cocaine and the composite "any illicit drug" category when drug involvement is binary for use (0–1) and A/D (0–1). Continuation ratio (CR) for ordinal variable for drug involvement (0–1–2)

	Any drug			Cannabis			Cocaine			Sedatives			Stimulants			Hallucinogens		
	Use OR	A/D OR	CR	Use OR	A/D OR	CR	Use OR	A/D OR	CR	Use OR	A/D OR	CR	Use OR	A/D OR	CR	Use OR	A/D OR	CR
Demographic																		
Age (years)	**0.97**	1.01	**0.02**	**0.97**	1.00	0.02	**0.99**	1.02	0.03	**1.01**	1.02	0.02	**1.00**	1.04	0.03	0.98	1.04	0.04
Education	1.02	**0.91**	**−0.11**	1.02	0.92	**−0.10**	0.95	0.97	−0.02	0.94	0.91	−0.09	0.96	0.95	−0.05	0.98	0.83	−0.18
Family income	**1.81**	**0.80**	−0.31	**1.15**	0.86	**−0.22**	1.06	0.74	**−0.31**	1.00	0.98	−0.02	1.01	0.77	−0.27	0.99	0.8	−0.22
Individual income	**1.34**	0.89	**−0.26**	**1.31**	0.87	**−0.27**	1.20	0.92	**−0.83**	1.06	0.76	−0.28	1.09	0.97	−0.04	1.15	0.89	−0.13
Divorce	**1.74**	1.29	−0.03	**1.71**	1.00	−0.22	**1.89**	**1.95**	0.58	**2.56**	1.19	0.10	**2.13**	1.03	−0.05	**1.89**	1.71	0.47
Cohabitation	0.99	1.04	0.04	0.99	1.13	0.12	1.04	0.54	**−0.62**	1.27	1.4	0.32	1.15	0.80	−0.24	0.96	0.39	−0.95
Religiosity																		
Personal devotion	**0.61**	0.98	**0.23**	**0.61**	0.98	**0.22**	**0.60**	1.45	**0.44**	0.77	1.21	0.21	**0.73**	0.73	−0.28	**0.68**	1.36	0.35
Personal conservatism	**0.83**	0.93	0.03	**0.82**	0.92	−0.08	**0.80**	0.97	0.01	**0.88**	0.76	−0.26	0.84	**0.88**	−0.11	**0.73**	1.05	0.08
Institutional conservatism	**0.73**	0.87	0.01	**0.72**	0.89	−0.05	**0.72**	0.88	−0.08	**0.80**	0.82	−0.18	**0.76**	**0.80**	−0.20	**0.75**	0.73	−0.29
Personality measures																		
Mastery	1.05	0.87	−0.16	1.05	0.86	−0.17	1.20	0.76	−0.31	0.92	1.0	0.01	1.09	**0.65**	**−0.44**	0.92	0.76	−0.27
Optimism	0.94	**0.81**	**0.19**	0.96	**0.76**	**−0.03**	0.94	0.78	−0.24	0.85	1.41	−0.35	0.89	0.71	−0.34	0.83	0.73	−0.29
Extraversion	**1.35**	0.96	**−0.19**	**1.34**	0.95	**−0.19**	**1.38**	0.89	−0.17	1.00	1.41	−0.35	1.00	0.78	−0.25	1.13	1.04	0.03
Neuroticism	**1.18**	1.20	0.10	1.16	1.19	0.10	1.12	1.36	0.29	1.29	1.05	0.03	1.17	1.27	0.22	1.26	1.28	0.22
Locus-of-control	1.03	**0.80**	**−0.23**	1.02	0.86	−0.16	1.06	0.78	−0.26	0.96	0.52	0.64	0.89	0.75	−0.27	1.03	0.67	−0.40
Self-esteem	0.98	0.83	**0.18**	0.98	0.83	**−0.18**	1.01	0.70	−0.36	0.83	1.28	0.27	0.98	**0.57**	**0.56**	0.83	1.06	0.08
Interpersonal dependence	1.11	1.12	−0.07	1.10	1.20	0.14	1.02	1.24	0.22	1.20	1.05	0.04	1.00	1.45	**0.37**	1.03	1.13	0.12
Altruism	**0.85**	0.94	0.02	**0.85**	0.91	−0.02	0.89	0.98	−0.07	0.95	1.13	0.13	0.87	0.92	−0.08	**0.78**	0.95	−0.02
Novelty-seeking	**1.62**	1.17	−0.09	**1.62**	1.11	−0.12	**1.54**	0.90	−0.16	**1.54**	0.81	−0.24	**1.36**	0.88	−0.16	**1.50**	**0.56**	**0.62**
Childhood factors																		
Childhood sexual abuse	**1.71**	**1.97**	0.41	**1.74**	1.59	0.20	**1.68**	**2.73**	**0.93**	**2.37**	2.51	**0.85**	**2.12**	**3.11**	**1.06**	1.84	**5.35**	**1.61**
Parental warmth	**0.85**	**0.80**	−0.14	**0.85**	0.87	−0.06	0.90	**0.70**	**−0.35**	0.79	0.83	−0.17	**0.82**	**0.62**	**−0.47**	**0.79**	0.81	−0.18
Psychiatric disorders																		
Bulimia	1.73	1.64	0.22	1.70	1.38	0.07	1.84	1.66	0.42	1.63	1.89	0.60	1.37	1.72	0.51	1.43	1.86	0.58
CD	2.40	0.74	−0.74	1.99	1.19	−0.16	1.05	0.84	−0.18	2.66	0.25	−1.47	1.51	0.18	−1.71	2.26	0.68	−0.48
GAD	1.36	**2.16**	**0.62**	1.19	**2.21**	**0.71**	**1.81**	**1.98**	0.60	**2.48**	1.02	−0.05	**1.81**	**0.81**	−0.09	1.73	**1.90**	0.59
Panic disorder	**1.78**	**2.79**	**0.74**	**1.71**	**3.23**	**0.91**	1.70	**2.09**	0.66	**3.59**	0.98	−0.12	**1.93**	**3.00**	**1.06**	**2.19**	**2.78**	**0.94**
Phobia	**1.51**	**1.70**	0.32	1.47	1.57	0.27	1.52	1.35	0.24	**2.07**	0.99	−0.06	1.73	1.78	0.52	1.44	1.55	0.40
MD	**1.81**	**2.28**	**0.53**	1.61	**2.17**	0.55	**1.93**	2.16	0.12	2.32	**3.26**	**1.21**	**2.11**	1.48	0.31	**2.26**	1.36	0.22

Note: Table 3 presents odds ratios (ORs) for the association between individual risk factors and a binary definition of drug use and abuse/dependence (A/D). The continuation ratio (CR) was calculated for each risk factor when drug involvement was coded as a three-level (0 = no use, 1 = use but no A/D and 2 = use and A/D) ordinal variable. Highlighted ORs and CRs were statistically significant after correction for multiple testing.

as well as the transition from use to abuse/dependence, as noted by positive CR (Table 3: CR = 0.44–0.80).

Personality measures

Elevated levels of novelty-seeking (NS) were positively associated with initiation of illicit drug use (Table 3: OR = 1.36–1.62). With the exception of hallucinogen abuse/dependence, levels of NS were unrelated to progression. With rare exception, levels of mastery and interpersonal dependence were unrelated to initiation or progression. In contrast, extraversion and altruism were significantly and positively associated with initiation of any drug, cannabis and cocaine (Tables 2 and 3). On the other hand, optimism, locus-of-control and self-esteem had a different pattern of association.

In a majority of cases, the CRs confirmed the results from the ORs. For instance, for novelty-seeking, extraversion and altruism, CRs were negative (but not statistically significant) suggesting that these personality measures were more closely associated with illicit drug initiation than with progression from use to abuse/dependence. In contrast, positive and significant CRs were noted for self-esteem (with some exceptions) which suggested that self-esteem was associated with progression to abuse/dependence for illicit drugs.

Childhood factors

A striking pattern emerged for childhood sexual abuse (CSA) and its relationship with drug involvement (Table 2). Fairly consistently, CSA was positively associated with illicit drug use (OR = 1.68–2.37) and with illicit drug abuse/dependence (OR = 1.97–5.35) with ORs being higher for abuse/dependence than for use. From Table 3, we see that the OR for CSA and cocaine use was 1.68 and the CR for CSA and cocaine abuse/dependence was 2.73. Also, the association between CSA and cocaine involvement (0 = never used cocaine, 1 = used cocaine, 2 = use and abuse/dependence of cocaine) was positive (CR = 0.93). Therefore, CSA was associated with use and abuse/dependence of cocaine, but had a more significant association with the transition from cocaine use to abuse/dependence than for the initiation of cocaine use.

As expected, high parental warmth was negatively correlated with use and abuse/dependence of any illicit drug. While not significant, the negative CR indicated that parental warmth was more closely associated with drug initiation than progression to abuse/dependence.

Psychiatric diagnoses

The most interesting results for this study were observed for the relationship between illicit drug involvement and psychiatric disorders. Anxiety disorders, especially panic disorder, were positively correlated with illicit drug use

(OR = 1.71–3.59) and, in some cases, abuse/dependence (OR = 2.09–3.23). The effect sizes of the OR suggested that statistical significance for some of these associations may be dependent on sample sizes. Major depression was also positively associated with use and abuse/dependence of any illicit drug and cocaine and with use of cannabis, sedatives, stimulants and hallucinogens (Table 2). Bulimia nervosa was unrelated to illicit drug use or abuse/dependence. Additionally, we found no evidence for a statistically significant association between conduct disorder and illicit drug involvement.

The CRs were useful in clarifying some of the associations between psychiatric illness and illicit drug involvement. For all the psychiatric disorders, with the unique exception of conduct disorder, CRs were positive (Table 3). The positive CR indicated that while psychiatric illness, such as anxiety disorders and major depression, may correlate with one or both stages of drug involvement, their strongest relationship was with the transition from illicit drug use to abuse/dependence. Conduct disorder, in contrast, presented with negative CRs (not significant), suggesting that while most Axis I disorders were closely related to progression to abuse/dependence, conduct disorder may play a substantial role in illicit drug initiation.

Overall, this study presents the following key findings:

(1) The ORs suggest that socio-demographic factors (e. g., income and divorce), measures of religiosity and certain personality measures reflecting impulse-disinhibition (e. g., novelty-seeking and extraversion) are strongly correlated with illicit drug use and only rarely associated with the abuse/dependence of illicit drugs.

(2) Measures of personality related to self-control and image (e. g., self-esteem and locus-of-control) are associated with abuse/dependence.

(3) Psychiatric diagnoses (e. g., anxiety disorders, major depression) and childhood risk factors of childhood sexual abuse and parental warmth are associated with illicit drug use and abuse/dependence.

(4) If drug involvement is represented by a single variable that accommodates use and abuse/dependence, the CRs suggest that psychiatric disorders are strongly associated with progression from illicit drug use to abuse/dependence. In contrast, the CRs for the socio-demographic variables suggest that risk factors, such as income, divorce and age, play a greater role in illicit drug initiation rather than progression to abuse/dependence.

(5) Interestingly, these trends of associations were observed to be fairly similar across pharmacologically different classes of illicit drugs (Table 2).

Discussion

The study of illicit drug involvement requires the consideration of risk factors that associate with one or more

stages of the process of drug involvement. While some risk factors may be associated specifically with drug use, others may be correlated with abuse/dependence. In this manuscript, we sought to examine the association between 26 putative risk factors and illicit drug involvement using two related techniques. First, we employed a dichotomous definition of drug use and abuse/dependence, where the association between risk factors and drug involvement was studied independently for drug use and drug abuse/dependence. Second, we used a single ordinal variable that represented drug involvement as a three-stage process marked by drug abstinence, drug use and drug abuse/dependence. The continuation ratio (CR) was used to measure whether a risk factor had a differential impact on initiation (abstinence to use) vs. progression (use to abuse/dependence).

Most of our findings are supported by the existing literature. We observed an association between income, education, age and divorce with illicit drug use. The relationship between socio-demographic measures, such as divorce and illicit drug involvement has been previously noted (Schwarz and Wheeler 1992; Davis and DiNitto 1996; Fu and Goldman 2000; Horwitz et al. 1996). Fu et al. observed that marital dissolution is positively associated with smoking, drug use and risky behavior in males and females (Fu and Goldman 2000). On the other hand, two studies note that the relationship between divorce or marital discord and drug involvement is stronger in females than males (Davis and DiNitto 1996; Horwitz et al. 1996). Our analyses suggest a positive association between divorce and drug use. However, due to the single wave of data, we cannot be certain of the directionality of causation, if any, which may explain this association. For instance, use of an illicit drug may result in marital conflict and culminate in divorce. On the other hand, marital discord and divorce may lead to depression and ultimately result in drug use. A similar set of alternative hypotheses are often used to explain the association between income or employment and drug involvement, which was also observed in our data. The social causation (loss of income causes drug misuse) and social stress (drug misuse causes loss of income) hypotheses may be used to explain the positive relationship between loss of income and drug abuse/dependence noted for the "any illicit drug" category (Dohrenwend 2000; Johnson et al. 1999). However, in contrast to previous studies suggesting that income is negatively associated with drug use, our data suggest that income is positively associated with drug use and negatively associated with abuse/dependence. One explanation for this may be the modestly higher socio-economic status of our dataset when compared to other epidemiological datasets or the inclusion of prescription drugs in the "any illicit drug" category which are relatively costly.

The religiosity measures indicated a strong negative association between religious beliefs and illicit drug use. A study of adolescents in the National Comorbidity Survey suggests a strong correlation between personal devotion and illicit drug use (Miller et al. 2000). Religiosity often acts as a "buffering" agent against stressful life events which may further predispose an individual to use or misuse a drug (Kendler et al. 1997, 1999). Additionally, religious affiliations and orthodoxy have a buffering effect on drug initiation (Gorsuch and Butler 1976b). Higher levels of personal devotion are associated with a lowered sensitivity to stress and its effects (Williams et al. 1991; Maton 1989; Krause and Van Tran 1989; Pressman et al. 1990). Most of the drugs show a strong positive association with the measures of high religiosity. A similar pattern is seen with nicotine and alcohol (Miller et al. 2000). An additional finding from this study is that measures of religiosity, especially personal devotion, are closely associated with initiation of drug use and that this relationship is stronger than the relationship between religiosity and abuse/dependence. In other words, high levels of personal devotion play a role in abstinence from use of illicit drugs.

The most striking risk factor that was significantly associated with all categories of drug use was novelty-seeking which is characterized by risk-taking behavior that anticipates a rewarding sensation. This follows the hypothesized pattern of perceived risk and reward. The initial stimulus to try a drug is dependent on the individual's ability to overcome social, religious and cultural inhibitions (impulse-disinhibition) (Pulkkinen and Pitkanen 1994) and ignore legal implications (Zuckerman 1983, 1987a, 1987b; Windle et al. 1989; Conrod et al. 2000). High levels of novelty-seeking and neuroticism are associated with increased MDMA use in males enrolled in compulsory military service (Bobes et al. 2002). In our study, extraversion was associated with initiation of any drug, cannabis and cocaine. This may be because an extraverted individual is more likely to obtain an illicit drug through an extensive peer-network.

We also observed that power-related personality measures like optimism and locus-of-control were associated with progression to abuse/dependence. Drug abuse and dependence is marked by deterioration of voluntary control over drug habits. Individuals repeatedly use drugs at the stage of dependence to escape the debilitating effects of withdrawal. Similarly, with increasing drug tolerance, there is repeated drug consumption to satiate need and experience the pleasurable effects of the drug that the individual has grown accustomed to. This constitutes a loss of self-control and may provide an explanation as to why personality-like measures that relate to an individual's idea of how much they control the events influencing their lives is inversely associated with drug progression. A similar significant association was seen for self-esteem with progression to abuse/dependence (Gossop 1976).

Childhood sexual abuse (CSA) was positively associated with illicit drug use and abuse/dependence, and the CR suggested that the magnitude of the association between CSA and progression from use to abuse/dependence is significant. Several studies, including a meta-analysis have examined the relationship between CSA

and psychological distress and psychiatric illness (Rind et al. 1998; Jumper 1995; Neumann et al. 1996; Kendler et al. 2000). Five prior studies present high odds ratios suggesting a strong association between presence of a prior history of CSA and drug use and abuse (Kendler et al. 2000; Bifulco et al. 1991; MacMillan et al. 1997; Martin et al. 1993; Fergusson et al. 1996). CSA independently, significantly and increasingly (the more severe the CSA, the higher the association) associates with drug abuse (Kendler et al. 2000; Martin et al. 1993; Bushnell et al. 1992). Our results support the previous findings with ORs ranging from 1.71 to 2.37 for drug use and higher ORs (1.97–5.35) for abuse/dependence. Along with the positive CR, our study suggests that CSA is associated with use of illicit drugs and also with progression from use to the pathological stage of abuse/dependence. On the other hand, parental warmth, which is a measure of the support and affection provided by parents, is a protective factor and is associated with lowered incidence of illicit drug use and abuse/dependence. However, in contrast to CSA, parental warmth is associated with the proximal stage of drug initiation rather than abuse/dependence.

The psychiatric diagnoses, especially anxiety disorders and depression, were positively associated with illicit drug use and abuse/dependence. The comorbid occurrence of depression or anxiety and drug misuse has been previously noted (Tsuang et al. 2001; Kandel et al. 1997, 1999; Regier et al. 1990). Also, Merikangas and colleagues have noted that the association between psychiatric disorders and drug involvement increases as the relative pathology of the stage in the drug habit increases and this finding was supported by our data (Merikangas et al. 1998). One possible pattern of association between illicit drug involvement and the anxiety and depressive disorders is that while psychiatric illness is associated with the onset or initiation of drug use (e. g., depression and sedative use) as well as the progression from use to abuse/dependence (cocaine abuse and panic disorders), the relationship between psychiatric illness and abuse/dependence is stronger. This correlation between pathological states could represent feedback loops whereby illicit drug use may occur as a result of depression and self-medication due to depression may result in misuse of the drug and lead to abuse/dependence, which in turn may lead to further depressive symptomatology. However, our results cannot be extrapolated to make causal inferences. We only propose the comorbidity model as a possible explanation for the association between psychiatric illness and illicit drug involvement.

A negative finding from our study was the lack of association between conduct disorder and illicit drug involvement. As noted in three detailed reviews of the literature, conduct disorder (CD) and its interaction with attention-deficit hyperactivity disorder (ADHD) is often proposed as a risk factor for illicit drug involvement (Flory and Lynam 2003; Armstrong and Costello 2002; Silberg et al. 1996). While the ORs were substantial

(OR = 1.05–2.66), the association between CD and illicit drug use or abuse/dependence was not statistically significant. There are two possible explanations for this. First, CD was coded as a binary variable and this dichotomization may have led to loss of statistical power. Second, the dichotomization coupled with the low prevalence of CD in females may be responsible for the lack of power to detect a significant association between CD and illicit drug involvement. Despite the lack of association, CD has a unique relationship with drug involvement. In contrast to anxiety and depression, which tend to associate more closely with the distal stage of illicit drug abuse/dependence, CD tends to be correlated with the initiation of illicit drug use. While our study cannot formally verify this finding, Silberg and colleagues, in a related dataset, show a similar pattern of associations. In a multivariate genetic study of adolescent male and female twins, Silberg et al. noted that CD tends to precede substance use, while depression tends to follow it (Silberg et al. 2003). Our CRs reflect a similar pattern, whereby CD is associated with initiation of illicit drug use (negative CR) and depression is associated with use and abuse/dependence, although its association with progression from use to abuse/dependence is stronger (positive CR).

Our study of illicit drug involvement and its relationship to putative risk factors examined associations, not causal pathways. Based on these correlations between risk factors and multiple stages of illicit drug involvement, we may propose that different risk factors have varying relationships with the multiple stages of drug involvement. Illicit drug use, which is a proximal stage in the process of drug involvement, is related to socio-economic variables, religiosity and risk-seeking behavior, while drug abuse/dependence, which is a distal stage in the process of drug involvement, associates with psychopathology and personality measures that index loss of control. Risk factors that are indicative of early influences (e. g., religious devotion or novelty-seeking) or refer to social change (e. g., divorce or loss of income) tend to be associated with illicit drug initiation. Furthermore, drug initiation is influenced by a larger set of specific factors than abuse/dependence and this may be due to the specific physiological and behavioral changes that accompany symptoms of abuse/dependence. Therefore, intense stressors (e. g., childhood sexual abuse) and psychopathology (e. g., anxiety disorders) are closely related to progression from a non-pathological stage of drug use to the distal stage of abuse/dependence.

■ Limitations

The results of this study must be viewed with the following limitations in mind. First, this study only included Caucasian female twins and may not be extended to other ethnicities. We were unable to compare sexes because several of the associated factors have not been measured in the male twins. Second, due to the absence

of multiple waves of data, the specific causal relationships between risk factors and drug involvement were not examined (Kraemer et al. 1997, 2001). Third, our measures of drug use and abuse/dependence are based on responses obtained from the participant during face-to-face interviews and subsequent telephone follow-ups. There may have been misinterpretation of questions or complete denial of drug use. This limits the reliability and validity of the reports of the participants. However, prevalence of drug initiation and progression reported in this study are fairly close to those reported by national surveys. Finally, this study uses female twins, both identical (MZ) and fraternal (DZ) as an epidemiological sample. Twins are emotionally and behaviorally similar to the general population and can be employed for an epidemiological study if twin correlations can be accounted for. This has been confirmed by several reports (Moilanen et al. 1999; de Geus et al. 2001; Kendler et al. 1995; Rutter and Redshaw 1991).

Conclusions

Why is it important to partition risk factors into those that correlate with illicit drug use and those that correlate with illicit drug abuse/dependence, even when the data are not informative in the interpretation of causality? First, our analyses provide a broad overview of the associations between risk factors and drug involvement and suggest that, while illicit drugs may be pharmacologically distinct, the risk factors that correlate with them may follow similar trends for all psychoactive substances. This, in turn, may reflect a general level of problem behavior (Jessor and Jessor 1977). For instance, a general liability to deviancy may explain the correlation between use of illicit drugs (any illicit drug), high novelty-seeking scores and lowered educational attainment. Second, these associations could also indicate causal relationships that are confounded by feedback mechanisms. For instance, an individual with high neuroticism scores may be predisposed to major depression as well as sedative use. In turn, the two resulting phenotypes could be comorbid or have causal impacts on each other. Therefore, while one model could reflect self-medication of depressive symptoms with sedatives, yet another may involve misuse of sedatives leading to major depression. Additionally, both models could influence the levels of neuroticism in the individual. While the current study is unable to test such causal models, the associations presented in this study provide interesting clues toward the development of potential models that may be tested with data from multiple occasions of measurement. With the appropriate data, one could establish whether low income causes cannabis use or is a result of cannabis use, or whether low income and cannabis use are correlated and caused by a third unknown variable, such as affiliations with a deviant peer network. One of the key applications of our findings will be in modeling the role of genes and environment within the associations observed in this study. A multivariate study including all 26 risk factors as well as drug use and abuse/dependence would be cumbersome and fairly uninformative. Our epidemiological findings may be used to select variables that may show genetic or environmental overlap with illicit drug involvement. Furthermore, some of the psychiatric diagnoses or personality variables may share latent risk factors (genetic or environmental) with drug use and/or abuse/dependence and the present study emphasizes the need for two-stage modeling of these bivariate and multivariate relationships. For instance, if genetic factors are shared by drug use and novelty-seeking and if drug abuse/dependence is not conditioned on prior drug use, then spurious genetic correlations may arise between novelty-seeking and drug abuse/dependence even when the relationship between personality and drug involvement is strongest for the proximal use stage. Behavior genetic extensions of the CR may be employed to resolve such confounding effects. Finally, this study is limited to a female sample. While this may be considered a limitation, this study adds to a fairly small set of analyses that examines drug habits in females and will be informative in the elucidation of gender differences when the relevant variables are available in males.

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