Predictors of Illicit Substance Dependence Among Individuals With Alcohol Dependence*

NICOLE D. SINTOV, M.A., KENNETH S. KENDLER, M.D.,[†] DERMOT WALSH, M.D.,[†] DIANA G. PATTERSON, M.D.,[†] AND CAROL A. PRESCOTT, PH.D.[†]

Department of Psychology, University of Southern California, Los Angeles, California 90089-1061

ABSTRACT. Objective: Individuals with alcohol dependence (AD) are at increased risk for developing dependence on illicit and prescription drugs. The goal of this cross-sectional study was to identify factors associated with drug dependence among individuals with AD. **Method:** The sample consisted of 855 adults from the Irish Affected Sib Pair Study of Alcohol Dependence who were treated in inpatient or outpatient alcohol treatment programs and met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, criteria for lifetime AD. We studied predictors of dependence on six classes of drugs: cannabis, sedatives, stimulants, cocaine, opioids, and hallucinogens. Potential predictors examined included gender, age, education, and socioeconomic status; the personality traits of extraversion, neuroticism, and novelty seeking; conduct disorder, major depressive disorder, nicotine dependence, age

at onset of alcohol use, early illicit drug use, and parental AD. **Results:** Nicotine dependence, depression that began before substance use, and drug use before age 19 each increased the risk for dependence on several substance classes. Male gender, younger age, maternal AD, fewer years of education, higher neuroticism scores, conduct disorder, and early alcohol use each increased the risk of dependence on one or more substance classes. **Conclusions:** Among individuals in treatment for AD, cigarette smoking, early onset of major depression, and early drug use were associated with increased risk for drug dependence. These results suggest individuals with these risk factors may benefit from more intensive screening to prevent the onset of or to identify and treat drug dependence. (*J. Stud. Alcohol Drugs* 70: 269-278, 2009)

AMONG INDIVIDUALS WITH ALCOHOL ABUSE or dependence, the prevalence of additional substance use disorders (SUDs) is high. For the purposes of this article, *SUD* refers to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV; American Psychiatric Association, 1994), illicit substance abuse or dependence, and *illicit* describes substances scheduled under the U.S. Controlled Substances Act, as well as nonmedical use of prescription psychotropic drugs. For instance, the National Longitudinal Alcohol Epidemiologic Survey (NLAES), a nationally representative household survey of 42,862 adults conducted in the United States, found that individuals with lifetime alcohol-use disorders (AUDs; alcohol abuse or dependence) were approximately 9-17 times more likely than those without AUDs to also meet criteria for a lifetime SUD (Grant and Pickering, 1996). Similar results were obtained in the National Comorbidity Survey (NCS), an epidemio-

logic sample of 8,098 individuals ranging in age from 15 to 54 years (Kessler et al., 1997). Among respondents who met DSM, Third Edition, Revised (DSM-III-R; American Psychiatric Association, 1987), criteria for lifetime alcohol dependence (AD), females with lifetime AD were 15.8 times as likely as females without lifetime AD to also have a lifetime SUD; males who met lifetime criteria for AD were 9.8 times as likely as males without AD to meet lifetime criteria for an SUD. Rates of SUDs are also elevated in clinical samples. For example, in a clinical sample of 248 individuals in treatment for AD, 64% also met lifetime criteria for an SUD (Staines et al., 2001).

SUDs are observed among approximately half of alcohol-dependent individuals (Kessler et al., 1997; Staines et al., 2001). This presents difficulties for a large portion of those who seek AD treatment because AD, when comorbid with SUDs, tends to follow a worse course and has a poorer response to treatment, including both unfavorable alcohol- and drug-related outcomes (Brown et al., 1998; Compton et al., 2003; Kranzler et al., 1996). In addition to elucidating the etiology of AD-SUD comorbidity, it is therefore important to identify factors that predict illicit substance dependence so that individuals characterized by such factors can be identified and receive treatment. Predictors identified in prior research include personality traits, comorbid psychopathology, smoking, early onset of alcohol and drug use, family history of alcoholism, and demographic characteristics. We briefly review selected evidence for each of these.

Received: January 22, 2008. Revision: October 2, 2008.

*This research was supported by National Institutes of Health grant R01-AA-11408 and the University of Southern California Annenberg Fellowship. Support for data collection was also provided by the Irish Health Research Board and Shaftsbury Square Hospital.

[†]Correspondence may be sent to Carol A. Prescott at the above address or via email at: cprescot@usc.edu. Kenneth S. Kendler is with the Virginia Institute for Psychiatric and Behavioral Genetics, Department of Psychiatry, Virginia Commonwealth University, Richmond, VA. Dermot Walsh is with the Health Research Board, Dublin, Ireland. Diana G. Patterson is with the Shaftsbury Square Hospital, Belfast, Northern Ireland.

Personality

Cross-sectional and longitudinal studies have found high levels of both neuroticism and novelty seeking to be associated with elevated risk of AUDs and SUDs (Chassin et al., 2004; Elkins et al., 2006; Iacono et al., 1999; Khan et al., 2005). A prospective investigation found that high neuroticism and high novelty seeking at age 17 significantly predicted new onsets of AUDs, SUDs, and tobacco use disorders by age 20 (Elkins et al., 2006). In another longitudinal study, participants with high novelty seeking scores in early adolescence or high neuroticism scores in young adulthood had higher risk for drug dependence or comorbid alcohol–drug dependence in later adulthood (Chassin et al., 2004).

Comorbid psychopathology

Comorbid AD and SUDs are also associated with increased prevalence of other forms of psychopathology, including childhood conduct disorder (CD) and lifetime depression (Goldstein et al., 2006; Grant et al., 2004; Kandel et al., 2001; Nock et al., 2006). In the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), respondents with antisocial personality disorder, which by definition requires a history of CD, were 1.5 times as likely as those without antisocial personality disorder to have a lifetime SUD (Goldstein et al., 2006). CD was assessed as part of the National Comorbidity Survey Replication study, a nationally representative household survey of 3,199 adults in the United States (Nock et al., 2006). In this sample, compared with individuals who did not meet criteria for childhood CD, those who reported childhood CD were 8.4 times more likely to have drug dependence.

Epidemiological studies have found strong associations between depression and SUDs. In the NESARC, approximately 20% of individuals with a past-year SUD also met the criteria for past-year major depression (Grant et al., 2004). In terms of risk, individuals with past-year drug dependence were nine times as likely to meet criteria for past-year major depression compared with those without drug dependence (Grant et al., 2004). In addition, 16% of respondents with past-year drug dependence also met past-year criteria for major depression in the Canadian Community Health Survey, a large, nationally representative survey of 36,984 individuals (Currie et al., 2005). Viewed another way, drug dependence was more than four times as likely among depressed individuals relative to nondepressed individuals (Currie et al., 2005). Also, results from the National Household Survey on Drug Abuse, a large, nationally representative survey conducted in the United States, are particularly germane to the present investigation (Kandel et al., 2001). Findings from this study indicated that of adults who were dependent on both alcohol and an illicit substance in the prior year, approximately 21% also met criteria for a past-year major

depressive episode. Relative to those who were not alcohol or drug dependent, the risk for depression was increased more than threefold among this comorbid group.

The relationship between AD and depression has been found to vary, depending in part on the temporal onset of depression in relation to AD. In the NCS, primary depression was not a significant predictor for later AD (Kessler et al., 1997). However, in the Virginia Adult Twin Study of Psychiatric and Substance Use Disorders (VATSPSUD), primary depression significantly increased the risk of later AD, whereas primary AD did not predict later depression (Kuo et al., 2006). To address these etiological issues, the analyses for the present study will examine a definition of depression defined in terms of onset relative to drug use.

Smoking and nicotine dependence

In cross-sectional and longitudinal studies, rates of smoking and nicotine dependence are elevated among individuals with AD as well as those with SUDs. In a randomly selected community sample of 4,075 German adults, those classified as current daily smokers were 4.6 times more likely to meet criteria for AUDs or SUDs compared with those who were never classified as smokers (John et al., 2004). In addition, a prospective study of 1,709 adolescents ages 14–18 found that youth who smoked cigarettes three or more times per week at baseline were approximately seven times as likely to develop SUDs 1 year later compared with youth who smoked two or fewer times per week (Brown et al., 1996).

Onset age of alcohol and drug use

Earlier age at onset of alcohol use is associated with increased risk of later AD; less is known about the relationship between the initiation of alcohol use and dependence on illicit substances. Results of the NLAES (Grant and Dawson, 1997) and the National Longitudinal Survey of Labor Market Experience in Youth (Grant et al., 2001), a prospective study in which a representative sample of 12,686 adolescents was initially assessed in 1979, indicate that the odds of having lifetime AD decreased by 5%–14% for each increasing year of age at onset of alcohol use, depending on the follow-up time frame.

Fewer studies have explored the association between age at onset of substance use and later drug dependence. Using a longitudinal design, Sung et al. (2004) examined the relationship between age at first substance use and later substance dependence among a sample of 1,420 adolescents ascertained through household sampling methods in North Carolina (2004). This study found that, compared with individuals who first used a substance at age 14 or older, those who began drug use before age 13 were at increased risk for developing an SUD by age 16. This study is limited by the follow-up time frame, which may have precluded detection

of SUDs that occur after age 16. However, results from the NLAES indicated that the risk of meeting criteria for lifetime drug dependence decreased by 5% with each increasing year of drug use initiation (Grant and Dawson, 1998). Thus there is some evidence that earlier age at first illicit drug use is associated with higher risk for later SUDs.

Family history of alcohol dependence

A preponderance of evidence has demonstrated elevated rates of AD among those who have a family member with AD (Cotton, 1979), but less research has addressed the association between parental AD and offspring SUDs. One study found an eightfold increased risk of comorbid AUDs and SUDs among relatives of probands with AUDs compared with controls (Merikangas et al., 1998). In prospective studies, adolescents with a family history of AD are more often classified as dependent on alcohol, drugs, or both in young adulthood compared with those with no family history (Chassin et al., 2004; Sher et al., 1991).

Demographic characteristics

Demographic characteristics, including gender, age, educational attainment, and socioeconomic status, have been associated with SUDs. Males are generally more likely than females to meet criteria for lifetime drug dependence (Diala et al., 2004; Warner et al., 1995). However, in the NCS, females with AD were more likely than affected males to have lifetime drug dependence (Kessler et al., 1997). Younger age is associated with higher prevalences of lifetime drug dependence (Warner et al., 1995) and comorbid AUDs and SUDs (Stinson et al., 2006). Educational attainment was not significantly related to drug dependence in the NCS (Diala et al., 2004), but in the NESARC, the prevalence of comorbid AUDs and SUDs was positively associated with educational level (Stinson et al., 2006). Drug dependence was associated with lower household income among NCS respondents (Warner et al., 1995), and lower personal income was associated with comorbid AUDs and SUDs among NESARC respondents (Stinson et al., 2006).

Goals of the present study

Much evidence has demonstrated the relationship of AD and SUDs to a variety of psychiatric disorders, personality traits, substance use variables, and demographic variables. However, there is a relative dearth of information on predictors for illicit substance dependence for separate substance classes; studies have tended to combine multiple illicit substance classes into a single, heterogeneous category. The primary goal of the present study was to identify predictors of dependence on specific illicit substance classes among individuals with AD.

Method

Participants

The data for the current study were collected as part of the Irish Affected Sib Pair Study of Alcohol Dependence (IASPSAD), which is a larger project investigating genetic influences on AD in families with multiple affected siblings (Prescott et al., 2005). Data were collected in Ireland and Northern Ireland from 1998 to 2002. Probands were eligible for study inclusion if they met lifetime DSM-IV criteria for AD, reported having at least one sibling with alcoholism, and all four grandparents had been born in Ireland or the British Isles. Inclusion criteria for siblings were the same as for probands. All interviewed participants provided written informed consent.

The original sample comprised 1,248 participants. The sample used for the current investigation included 855 individuals from 547 families who reported participation in inpatient or outpatient treatment for alcoholism. We chose to include only participants who reported receiving treatment for alcoholism because we wanted to have a more clearly defined sample from which to generalize. For the same reason, we included only probands and their siblings, which excluded 10 participants who were alcohol-dependent fathers and uncles of probands. Sample characteristics are described in Table 1.

TABLE 1. Participant demographic characteristics and lifetime prevalences of comorbid disorders and other predictors ($N = 855$)

Variable	Females ($n = 294$)	Males ($n = 561$)
Demographics		
Age, in years, mean (SD)	42.6 (8.9)	42.4 (9.9)
Completed secondary education, % ^a	60.9	51.7
Paternal social class, mean (SD) ^b	3.8 (1.5)	4.0 (1.5)
DSM-IV disorder, %		
Conduct disorder	24.9	44.2
Primary depression	42.8	43.5
Nicotine dependence	65.5	68.1
Cannabis dependence	8.6	17.3
Sedative dependence	18.5	17.3
Stimulant dependence	5.5	11.5
Cocaine dependence	1.0	5.3
Opioid dependence	6.2	7.1
Hallucinogen dependence	0.7	4.2
Any substance dependence	27.6	30.0
Other predictors		
Neuroticism score, mean (SD)	8.5 (3.6)	8.2 (3.6)
Novelty seeking score, mean (SD)	10.0 (3.9)	10.5 (3.9)
Extraversion score, mean (SD)	4.6 (2.6)	4.3 (2.7)
Age at first drink, mean (SD)	16.7 (4.6)	14.9 (3.6)
Early drug use, %	20.4	30.5
Maternal AD, %	24.9	17.8
Paternal AD, %	59.6	54.2

Notes: DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; AD = alcohol dependence. ^aProportion who completed secondary school (O-levels); ^brange = 1-6, lower score indicates higher social class.

Measures

Study interviewers were trained psychiatrists, psychiatric nurses, psychologists, and social workers experienced in mental health or substance abuse treatment settings or interviewing work. Participants were usually interviewed in person at their homes or a treatment facility. Four percent of the sample was interviewed by telephone because they lived outside of Ireland or were unavailable for an in-person interview. Other details of the study procedures and ascertainment are available in Prescott et al. (2005).

Lifetime history of AD was assessed using a modified version of the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA Version 11; Bucholz et al., 1994), which provides for assessment of DSM-IV diagnostic criteria. Lifetime history of substance use and dependence was assessed for seven substance classes: cannabis, sedatives, stimulants, cocaine, opioids, hallucinogens, and other substances (e.g., inhalants, diet aids) using the Structured Clinical Interview for the DSM-III-R (SCID; Spitzer and Williams, 1985) adapted and used previously in other samples (Kendler and Prescott, 2006). The "other" category was quite heterogeneous, therefore we omitted it from the current analyses. Participants were shown a list of drugs and asked which they had ever used. These were then grouped into categories based on drug class and, for each category used, subsequent questions asked about age at first use and quantity of use. For each category of substance used 11 or more times, the participant was asked questions to evaluate the DSM-IV criteria for substance dependence. Test-retest reliability information is available for the interview based on a study of 383 VATSPSUD participants interviewed twice over an average interval of 6 weeks. The test-retest reliability for substance-dependence diagnoses was .65 for cannabis, .63 for sedatives, .70 for stimulants, .67 for cocaine, .77 for opioids, and .66 for hallucinogens (Kendler and Prescott, 2006).

Lifetime history of major comorbid conditions, including major depressive disorder and history of CD before age 15, was also assessed using the SCID. Test-retest reliability was .88 for major depression and .65 for CD in the VATSPSUD sample (Kendler and Prescott, 2006). Because the goal of our study was to identify predictors of drug dependence, we were interested in depression that began before problematic illicit substance use. We created a primary depression variable that was coded positive if the age at onset of depression was at least 1 year before the age at onset of any substance-dependence symptoms or if the participant did not report substance-dependence symptoms. The variable was coded as negative if the age at onset of depression was within 1 year of or later than the age at onset of substance-dependence symptoms or if depression was not present.

Nicotine dependence was assessed using a cutoff of 7 or greater on the Fagerstrom Test for Nicotine Dependence (Heatherton et al., 1991).

We include here as a covariate a binary variable of early drug use, coded 1 if the participant tried an illicit drug before age 19 and coded 0 otherwise.

Personality was assessed using the short form of Eysenck's Neuroticism and Extraversion scales (Eysenck et al., 1985) and the novelty seeking scale from the Tridimensional Personality Questionnaire (Cloninger et al., 1994).

Maternal and paternal AD were assessed using the Family History-Research Diagnostic Criteria probe structure (Andreasen et al., 1977), which asks if the relative has had alcohol treatment or if drinking caused problems at home, at work, with health, or with the police. Positive endorsements of this question led to six additional questions related to that relative's drinking, including drinking-related problems, out-of-control drinking, and treatment. In this sample, participant reports have previously been shown to have good interrater reliability and agreement with clinical assessments of parental AD (Prescott et al., 2005). The parental AD variables were coded as positive if the participant reported three or more symptoms of AD in the respective parent, and negative otherwise.

Demographic variables included the participant's age at interview, education level, and paternal social class. The educational attainment variable was coded as binary to indicate whether the participant completed secondary school. The participant's current social class was significantly correlated with substance dependence ($p = .14$, $p < .0001$), but it seemed likely that current social class represents an outcome rather than a predictor of substance involvement. Therefore, we elected to use paternal social class to approximate family of origin socioeconomic status for the period when the individual was at risk for initiating illicit drug use. Social class was rated using a manual specific to Ireland. Response values for paternal social class ranged from 1 to 6, with lower values representing higher social class.

Statistical analyses

The outcomes studied were dependence on six classes of drugs: cannabis, sedatives, stimulants, cocaine, opioids, and hallucinogens. All outcomes were coded as binary. Generalized estimating equation (GEE) analyses were conducted to identify the predictors of dependence for each of the six classes of illicit substances. Potential predictors were demographic variables, including gender, age, educational attainment, and paternal social class; the personality factors of extraversion, neuroticism, and novelty seeking; comorbid disorders and early use, including CD, primary depression, nicotine dependence, age at onset of alcohol use, and early drug use; and familial risk indicated by maternal AD and paternal AD. All analyses were performed using the SAS Version 9.1 software program (SAS Institute Inc., 2002). The SAS Genmod procedure was used to handle the correlated data from siblings. Correlated observations result

from clustered data, which occurs when participants are members of the same cluster. In the case of the present study, this situation arose because some participants were from the same families. Sib pair resemblance for the predictors ranged from $p = .01$ for novelty seeking to $p = .96$ for paternal AD. Correlated data can lead to underestimation of variance and spuriously low p values. GEEs correct for this by providing robust standard error estimates (Orelien, 2001).

Personality scores were transformed into z scores to facilitate interpretation, so that odds ratios (ORs) are comparable across all personality measures and reflect the odds for a 1 SD difference. Age cohort effects were investigated by including both linear and quadratic age terms. The quadratic effects were not significantly associated with any of the outcomes. Therefore, we do not report these results.

For each substance-dependence outcome, the same analytic procedures were followed. A hierarchical model building procedure was used to select variables for inclusion in the final set of models. Variables were separated into four conceptual blocks: demographics (gender, age, age squared, education, paternal social class), familial risk (maternal AD and paternal AD), personality factors (neuroticism, novelty seeking, and extraversion), and comorbid disorders and early use (CD, primary depression, nicotine dependence, early drug use, and age at onset of alcohol use). Each block of predictors was regressed on each outcome in a GEE model. Predictors that were significant ($p < .05$) in any block model were retained in the set of final models used to estimate the simultaneous effects of predictors. This procedure was used to ensure the inclusion of the same set of participants in each substance class outcome, and to facilitate interpretability of results. Extraversion, paternal social class, and quadratic age were not significant in their respective block models and thus were excluded from all final models. Based on prior research implicating gender differences in predictors for drug dependence, gender was assessed as a moderator of the relationship between each drug-dependence outcome with CD and primary depression. Separately for CD and depression, interaction terms and main effects were entered into GEE models for each substance-dependence outcome. Interaction terms significant for a given outcome were included in that final model.

A total of 49 participants had missing personality data owing to participants not completing these forms. In addition, 78 participants were missing maternal AD data and 81 were missing paternal AD data because of a change in study design in which this information was not collected for some participants. The results of chi-square tests of association indicated that prevalence of illicit drug dependence across the substance classes did not differ systematically between participants with versus without personality data, maternal AD data, or paternal AD data. The final GEE models are based on those participants who had complete data ($n = 743$).

Results

Sample demographic and personality characteristics, lifetime prevalences of drug dependence, comorbid psychopathology, and other predictors are presented by gender in Table 1. This is a severely affected sample. The mean (SD) number of DSM-IV alcohol-dependence symptoms was 6.6 (0.79). Participants reported that they consumed a mean of 17.6 (10.4) alcoholic drinks per day in the month before the interview. Approximately 31% and 42% of participants reported that drinking caused them liver damage and stomach disease, respectively.

Table 2 displays the ORs and Wald 95% confidence intervals (CIs) for all predictors and outcomes from the univariate models. Table 3 displays the ORs and CIs for the predictors that were significant in the univariate models and thus included in the set of final models. Based on the final models, the following significant results were found.

Cannabis

Male gender, younger age, primary depression, nicotine dependence, earlier age at first alcohol use, and early drug use each increased the odds of cannabis dependence. In addition, a Primary Depression $\times$ Gender interaction was found such that females with primary depression were more likely to have cannabis dependence than were males with primary depression (female OR = 6.08, 95% CI: 2.21-16.68; male OR = 1.48, 95% CI: 0.95-2.30).

Sedatives

Higher neuroticism scores, CD, primary depression, nicotine dependence, early drug use, and maternal AD use each significantly increased the odds of sedative dependence. In addition, Gender $\times$ CD and Gender $\times$ Primary Depression interactions were found. Primary depression increased the odds of sedative dependence among females (OR = 13.51, 95% CI: 5.84-31.26) more so than among males (OR = 2.92, 95% CI: 1.85-4.62). CD increased the odds of sedative dependence among males (OR = 3.40, 95% CI: 2.11-5.47) but not females (OR = 0.94, 95% CI: 0.47-1.87).

Stimulant dependence

Male gender, younger age, CD, primary depression, nicotine dependence, and early drug use each increased the odds of stimulant dependence.

Cocaine dependence

Early drug use significantly increased the odds of cocaine dependence.

TABLE 2. Odds ratios and 95% Wald confidence intervals for block models

Block	Predictor	Cannabis	Sedative	Stimulant	Cocaine	Opioid	Hallucinogen
Demographic (<i>n</i> = 837)	Gender	0.87* (0.35-1.41) <i>p</i> = .0012	0.91 (0.62-1.33) <i>p</i> = .62	0.72* (0.09-3.86) <i>p</i> = .025	4.82* (1.52-15.24) <i>p</i> = .007	1.17 (0.62-2.20) <i>p</i> = .63	5.64* (1.31-24.39) <i>p</i> = .02
		0.82 (0.64-1.05) <i>p</i> = .12	0.88* (0.78-0.98) <i>p</i> = .03	0.73* (0.61-0.88) <i>p</i> = .0009	1.20 (0.82-1.75) <i>p</i> = .35	1.13 (0.84-1.52) <i>p</i> = .42	1.16 (0.72-1.88) <i>p</i> = .54
		0.72 (0.43-1.19) <i>p</i> = .20	0.74 (0.49-1.11) <i>p</i> = .15	0.64 (0.37-1.10) <i>p</i> = .19	0.72 (0.37-1.39) <i>p</i> = .32	0.72 (0.40-1.29) <i>p</i> = .27	0.32* (0.13-0.83) <i>p</i> = .019
	Paternal SES	1.03 (0.86-1.24) <i>p</i> = .74	1.06 (0.93-1.20) <i>p</i> = .42	1.18 (0.97-1.44) <i>p</i> = .09	1.00 (0.79-1.26) <i>p</i> = .98	0.96 (0.76-1.21) <i>p</i> = .72	0.89 (0.70-1.14) <i>p</i> = .36
		1.25 (0.99-1.6) <i>p</i> = .06	1.65* (1.27-2.14) <i>p</i> < .0001	1.45* (1.07-1.96) <i>p</i> = .017	1.22 (0.87-1.71) <i>p</i> = .26	1.64* (1.12-2.40) <i>p</i> = .01	1.50 (0.82-2.76) <i>p</i> = .19
		1.86* (1.48-2.34) <i>p</i> < .0001	1.29* (1.05-1.58) <i>p</i> = .01	1.65* (1.27-2.14) <i>p</i> < .0001	1.52* (1.08-2.17) <i>p</i> = .02	1.46* (1.07-2.00) <i>p</i> = .017	1.45 (0.92-2.28) <i>p</i> = .11
	Extraversion	0.87 (0.69-1.10) <i>p</i> = .24	0.97 (0.79-1.19) <i>p</i> = .80	0.96 (0.74-1.25) <i>p</i> = .76	0.85 (0.56-1.29) <i>p</i> = .45	0.87 (0.64-1.17) <i>p</i> = .35	1.00 (0.60-1.66) <i>p</i> = .9969
		1.33 (0.84-2.10) <i>p</i> = .23	1.33 (0.87-2.04) <i>p</i> = .18	2.92* (1.56-5.46) <i>p</i> = .0008	2.38 (0.96-5.90) <i>p</i> = .06	2.16 (1.13-4.15) <i>p</i> = .02	1.27 (0.51-3.18) <i>p</i> = .61
		2.58* (1.64-4.07) <i>p</i> < .0001	8.67* (5.62-13.37) <i>p</i> < .0001	2.78* (1.52-5.07) <i>p</i> = .0009	1.24 (0.52-2.97) <i>p</i> = .63	2.61* (1.30-5.25) <i>p</i> = .007	2.15 (0.82-5.61) <i>p</i> = .12
	Nicotine dependence	1.99* (1.08-3.66) <i>p</i> = .03	2.01* (1.22-3.32) <i>p</i> = .006	2.82* (1.26-6.30) <i>p</i> = .0117	3.02 (0.82-11.14) <i>p</i> = .098	2.03 (0.90-4.57) <i>p</i> = .09	3.06 (0.67-13.91) <i>p</i> = .15
		0.85* (0.79-0.92) <i>p</i> < .0001	0.98 (0.92-1.04) <i>p</i> = .50	0.92 (0.85-1.01) <i>p</i> = .07	0.91* (0.83-0.99) <i>p</i> = .03	1.06 (0.96-1.17) <i>p</i> = .25	0.83* (0.73-0.95) <i>p</i> = .007
		5.13* (3.22-8.16) <i>p</i> < .0001	1.74* (1.07-2.84) <i>p</i> = .03	5.12* (2.88-9.11) <i>p</i> < .0001	6.98* (2.5-14.47) <i>p</i> = .0002	5.14* (2.57-10.29) <i>p</i> < .0001	5.57* (1.70-18.25) <i>p</i> = .0045
Comorbid risk (<i>n</i> = 839)	Conduct disorder	1.05 (0.62-1.78) <i>p</i> = .86	2.00* (1.27-3.15) <i>p</i> = .003	1.09 (0.56-2.12) <i>p</i> = .80	0.72 (0.23-2.24) <i>p</i> = .57	1.72 (0.88-3.36) <i>p</i> = .11	3.01* (1.21-7.47) <i>p</i> = .02
		0.41 (-0.04-0.85) <i>p</i> = .08	1.47 (0.98-2.21) <i>p</i> = .06	2.09* (1.19-3.66) <i>p</i> = .01	0.99 (0.46-2.13) <i>p</i> = .98	1.52 (0.83-2.78) <i>p</i> = .18	1.27 (0.50-3.26) <i>p</i> = .61
	Paternal AD						
Familial risk (<i>n</i> = 767)	Maternal AD						
	Paternal AD						

Notes: SES = socioeconomic status; AD = alcohol dependence.

*Significant at $\alpha = .05$.

Opioid dependence

Primary depression and early drug use significantly increased the risk for opioid dependence.

Hallucinogen dependence

Fewer years of education, early drug use, and maternal AD each increased the odds of dependence on hallucinogens.

Any substance dependence

We also explored as an outcome dependence on any of the six substance classes. Significant predictors included higher neuroticism scores, primary depression, nicotine dependence, early drug use, and maternal AD. Significant interactions of Gender $\times$ CD and Gender $\times$ Primary Depression that mirrored

the patterns observed for sedative dependence were found. Depressed females were at greater risk for substance dependence (OR = 9.67, 95% CI: 5.20-18.00) than were depressed males (OR = 2.31, 95% CI: 1.60-3.33), and males with CD were more likely to report substance dependence (OR = 3.50, 95% CI: 2.40-5.12) than were females with CD (OR = 1.97, 95% CI: 1.12-3.47).

Discussion

To our knowledge, this is the first study to examine predictors for dependence on multiple illicit substances in a treatment sample of alcohol-dependent individuals. Many of the potential predictors significantly increased the odds of drug dependence in this sample. Each predictor will first be considered individually. We then discuss how results for individual substance classes compared with our findings for

TABLE 3. Odds ratios and 95% confidence intervals based on final generalized estimating equation models of predictors of substance dependence ($n = 743$)

Predictor	Cannabis	Sedative	Stimulant	Cocaine	Opioid	Hallucinogen	Any
Gender	3.64* (1.33-9.88) $p = .011$	0.84 (0.30-2.39) $p = .75$	4.60* (1.11-19.08) $p = .04$	2.72 (0.80-9.19) $p = .11$	1.13 (0.57-2.25) $p = .73$	3.73 (0.93-14.90) $p = .06$	1.15 (0.56-2.38) $p = .70$
Age	0.93* (0.90-0.96) $p < .0001$	1.03 (0.99-1.06) $p = .052$	0.91* (0.86-0.96) $p = .0006$	0.98 (0.94-1.02) $p = .26$	0.99 (0.95-1.02) $p = .48$	0.93 (0.87-1.001) $p = .06$	0.99 (0.96-1.02) $p = .36$
Education	0.95 (0.53-1.69) $p = .86$	1.18 (0.74-1.89) $p = .49$	0.61 (0.31-1.20) $p = .15$	0.74 (0.40-1.37) $p = .34$	0.83 (0.44-1.59) $p = .58$	0.26* (0.09-0.78) $p = .02$	1.37 (0.87-2.13) $p = .17$
Neuroticism	1.10 (0.85-1.41) $p = .47$	1.67* (1.28-2.20) $p = .0002$	1.23 (0.88-1.72) $p = .23$	1.07 (0.72-1.59) $p = .74$	1.40 (0.98-1.99) $p = .06$	1.17 (0.63-2.18) $p = .61$	1.55* (1.25-1.92) $p < .0001$
Novelty seeking	1.33 (0.97-1.83) $p = .07$	1.05 (0.83-1.33) $p = .69$	1.01 (0.69-1.49) $p = .96$	0.93 (0.62-1.39) $p = .72$	1.22 (0.84-1.76) $p = .30$	0.89 (0.48-1.66) $p = .72$	1.05 (0.84-1.31) $p = .65$
Conduct disorder	1.00 (0.60-1.66) $p = .99$	0.36* (0.15-0.88) $p = .025$	2.14* (1.16-3.96) $p = .015$	2.37 (0.87-6.46) $p = .09$	1.71 (0.86-3.39) $p = .12$	0.75 (0.28-2.04) $p = .58$	0.61 (0.27-1.37) $p = .23$
Primary depression	5.14* (1.92-13.73) $p = .0011$	12.40* (4.96-31.04) $p < .0001$	6.77* (1.33-34.50) $p = .02$	1.35 (0.60-3.06) $p = .46$	2.38* (1.24-4.55) $p = .009$	2.45 (0.88-6.76) $p = .09$	11.84* (6.00-23.35) $p < .0001$
Nicotine dependence	2.16* (1.09-4.28) $p = .03$	2.01* (1.13-3.58) $p = .018$	4.00* (1.71-9.33) $p = .001$	2.04 (0.61-6.83) $p = .25$	1.64 (0.72-3.78) $p = .24$	1.74 (0.38-7.93) $p = .47$	1.75* (1.12-2.75) $p = .01$
Age at onset of alcohol use	0.88* (0.80-0.96) $p = .006$	0.94 (0.87-1.009) $p = .08$	0.98 (0.89-1.08) $p = .63$	0.94 (0.86-1.02) $p = .15$	1.09 (0.99-1.21) $p = .09$	0.86 (0.72-1.02) $p = .08$	0.94 (0.88-1.02) $p = .13$
Early drug use	4.11* (2.42-6.98) $p < .0001$	2.99* (1.71-5.24) $p = .0001$	3.61* (1.79-7.28) $p = .0003$	9.89* (3.17-30.92) $p < .0001$	6.53* (3.06-13.94) $p < .0001$	11.90* (1.89-74.99) $p = .008$	5.77* (3.56-9.37) $p < .0001$
Maternal AD	1.14 (0.61-2.13) $p = .67$	2.22* (1.29-3.80) $p = .004$	1.27 (0.60-2.67) $p = .53$	0.65 (0.22-1.93) $p = .44$	1.80 (0.86-3.79) $p = .12$	3.26* (1.25-8.48) $p = .02$	1.66* (1.02-2.69) $p = .04$
Paternal AD	1.04 (0.59-1.80) $p = .90$	1.34 (0.82-2.20) $p = .25$	1.91 (1.00-3.67) $p = .051$	0.78 (0.35-1.75) $p = .55$	1.18 (0.62-2.26) $p = .61$	0.88 (0.34-2.27) $p = .79$	1.13 (0.73-1.76) $p = .57$
Primary Depression $\times$ Gender ^a	-1.19 $p = .03$	-1.09 $p = .04$	-1.06 $p = .18$				-1.16 $p = .009$
Conduct Disorder $\times$ Gender ^a		1.96 $p = .0003$					1.23 $p = .01$

Notes: Variables were coded as follows: conduct disorder, primary depression, nicotine dependence, maternal alcohol dependence (AD), paternal AD; 0 = no, 1 = yes. Gender: 0 = female, 1 = male. Neuroticism and novelty seeking: z scores. Age and age at onset of alcohol use: continuous. Early illicit drug use: 0 = age 18 or younger, 1 = after age 18 or never. Education: 0 = did not complete secondary school, 1 = completed secondary school. A blank space signifies that a variable was not included in the final model for a particular outcome because of its lack of significance in the univariate model for that outcome. ^aRegression weights and standard errors are displayed for interaction terms. Odds ratios for each stratum are reported in the results section.

*Significant at $\alpha = .05$.

dependence on any substance, followed by clinical implications, and then study limitations.

Predictors and illicit drug dependence

Personality. In the present study, higher neuroticism scores increased the odds of dependence on sedatives (OR = 1.7). In addition, higher novelty seeking scores significantly increased the odds of all outcomes in the block models but failed to retain significance for any of the outcomes in the final set of models. The magnitude of the neuroticism effect is similar to the results obtained by Khan et al. (2005), who found that the odds of drug dependence were increased 1.6 times by higher neuroticism scores as well as by higher

novelty seeking scores. We found that only one outcome was predicted by neuroticism and none by novelty seeking, which contrasts with prior evidence that has shown these personality variables to be relatively broad predictors for substance dependence (Chassin et al., 2004; Elkins et al., 2006; Khan et al., 2005). However, these studies did not examine separate substance classes.

Comorbid psychopathology. In the present study, CD increased the risk for stimulant dependence (OR = 2.1) and for sedative dependence among males (OR = 3.4). These ORs are considerably lower than those reported previously by Nock et al. (2006), who found that individuals with a history of CD were 8.4 times as likely to meet criteria for drug dependence. The magnitude of our result may differ

from this previous finding because our sample comprised alcohol-dependent individuals who likely had less variation in outcomes than Nock et al.'s epidemiological sample. Also related, the OR we found may have been weaker because our sample of alcohol-dependent individuals was at the upper end of the distribution with regard to symptoms. More consistent with our finding, NESARC respondents with antisocial personality disorder, also at the upper end of the distribution of externalizing symptoms, were 1.5 times as likely to have an SUD compared with those without antisocial personality disorder (Goldstein et al., 2006).

In our sample, primary depression increased the risk of dependence on cannabis, sedatives, stimulants, and opioids (ORs = 5.1, 12.4, 6.8, and 2.4, respectively). These results are consistent with prior findings that depression increases the odds of substance dependence (Grant et al., 2004; Kandel et al., 2001). Our results add to the existing literature, because prior studies did not report on specific drugs and examined past-year depression and past-year substance dependence, whereas in the present study, lifetime disorders were assessed. Our findings indicate that primary depression in particular is a predictor for drug involvement, suggesting that individuals who use drugs to cope with depression may be at higher risk for developing drug dependence.

Nicotine dependence. In our sample, nicotine dependence significantly increased the odds of dependence on cannabis and sedatives by approximately twofold and stimulants by fourfold. These results augment earlier findings indicating that greater cigarette smoking increased the risk of later developing SUDs (Brown et al., 1996) and that nicotine dependence increased the odds of having either an AUD or SUD by 4.6 times (John et al., 2004).

Early drug use. Much of the prior literature has reported on associations between the age at onset of alcohol use and the risk of developing AD (e.g., Grant and Dawson, 1997; Grant et al., 2001), but few studies have discussed age at onset of drug use and later substance dependence (Grant and Dawson, 1998). The present study identified early illicit substance use as a predictor common to all substance classes. It is important to note that as defined here, this variable serves as an indicator of early drug involvement and does not code for onset age of drug use. In our study, those who reported using a drug before age 19 were approximately 3%-12% more likely to develop substance dependence, depending on substance class, compared with those who never used drugs or who began doing so at or after age 19. Grant and Dawson (1998) found that the odds of developing drug dependence increased by 5% with each decreasing year of first drug use, but ORs for specific substances were not reported. Our findings could be important for intervention work, as others have argued that delaying the age of first substance use may reduce the risk of developing later substance dependence (e.g., Pedersen and Skrandal, 1998). Before this conclusion is drawn, however, future studies should examine more

closely the relationship between early drug involvement and illicit substance dependence to determine whether this is a causal relationship (e.g., Prescott and Kendler, 1999).

Demographic characteristics. The present study found that younger individuals were more likely than older individuals to be dependent on cannabis and stimulants. These findings are generally consistent with prior findings from the NCS and the NESARC indicating that younger respondents were more likely than older respondents to be drug dependent (Stinson et al., 2006; Warner et al., 1995).

Several gender differences were observed in the present study. First, males were more likely to be substance dependent than females. This differs from findings from the NCS, in which SUDs were more common among alcohol-dependent females than alcohol-dependent males (Kessler et al., 1997). The NCS did not report on specific substances, however; therefore, it is possible that some gender differences were lost in combining all substance classes together. It is also possible that ours being a treatment sample influenced our findings.

Another gender difference was that CD increased the odds of sedative dependence among males but not females. Conversely, primary depression increased the odds of cannabis and sedative dependence among females to a greater extent than among males. If a directional pathway from depression to drug dependence exists, it appears to be more potent for females than males. The finding regarding sedatives is likely the result of a combination of overuse of benzodiazepines to treat depression and anxiety in the 1980s and 1990s (particularly among women), the use of benzodiazepines to treat alcohol withdrawal symptoms, and the perception among women of sedatives as a more socially acceptable form of drug use.

Educational level was not associated with most outcomes, but not completing secondary school education significantly increased the odds of hallucinogen dependence by 3.8 times. Our results add to the mixed findings concerning the relationship between educational attainment and SUDs. Although educational attainment was not significantly related to drug dependence in the NCS (Diala et al., 2004), in the NESARC, the prevalence of comorbid AUDs and SUDs increased with increasing educational level (Stinson et al., 2006). One reason our results may differ is because we examined a treatment sample of alcohol-dependent individuals. In addition, we found that lower education level increased the odds of dependence on hallucinogens only, whereas the NCS and NESARC reported on the heterogeneous category of illicit drugs.

General versus substance-specific drug-dependence outcomes

Examining dependence on any of the six substance classes as an outcome, we found that nicotine dependence,

primary depression, early illicit drug use, higher neuroticism scores, and maternal AD each significantly increased the risk of dependence. These results mirror those for the sedative-dependence outcome, which had the greatest number of affected individuals. In general, more predictors from the block models retained significance in the final set of models for cannabis, sedatives, and stimulants, the outcomes with the highest prevalences, compared with cocaine, opioids, and hallucinogens. It is possible that the relatively small sample size for the latter outcomes reduced the power to detect effects. The NLAES and NESARC have found relatively greater prevalences of dependence on cannabis, cocaine, and prescription drugs compared with other drugs (Grant and Pickering, 1996; Stinson et al., 2006). Investigations of predictors for SUDs based on these samples have combined individual substance class outcomes into a single drug-dependence category. Detailed information may have been lost in doing this, and it is possible that characteristics of the users of the more prevalent drug classes drove the results of these prior studies.

Clinical implications

Intervention and screening efforts can be informed by these findings. However, the implications of the results probably vary by setting. By the time people are in treatment for AD, certain factors such as demographic variables, parental AD, and early age at onset of alcohol and illicit substance use are not useful for intervention. If the etiology between SUDs and comorbid psychopathology is shared, as has been suggested previously (e.g., Kendler et al., 2003), then predictors such as depression and nicotine dependence may serve as indicators of this underlying vulnerability and intervening might not alter the risk for SUDs.

It is important to note that SUDs are likely to complicate AD treatment. Consistent with prior findings, we found that drug dependence was associated with more severe AD (Kranzler et al., 1996). Individuals with drug dependence reported more DSM-IV AD symptoms and drank larger quantities of alcohol during their heaviest drinking period than did those without SUDs. Therefore, a thorough evaluation should be conducted so that SUDs can be identified and treated along with AD.

Study strengths and limitations

Our results should be considered in light of several factors. First, there are limits to the generalizability of findings based on a sample of Caucasian alcohol-dependent individuals residing in Ireland. It is possible that the results may not generalize to individuals in the community with untreated AD. However, alcoholism treatment is more accessible to individuals in Ireland and Northern Ireland because of government-sponsored health care. Consequently, this sample

may not have many of the limitations of a treatment sample ascertained in U.S. treatment settings. There may also be cultural differences in drug availability and acceptability in Ireland that influence the prevalence of substance use and dependence. For example, 29% of our sample had a history of drug dependence compared with 57% in a U.S. alcohol-dependent treatment sample (Staines et al., 2001). Second, the reliability and validity of assessments of lifetime symptomatology are limited by retrospective self-report, which is subject to memory bias.

This study had several strengths. To our knowledge, this was the first study to examine predictors of substance use disorders studied separately by drug class. In addition, the sample was relatively large and was well characterized in terms of comorbid disorders.

Future directions

Future investigations using longitudinal designs to study substance use disorders are needed to help elucidate the relationships between risk factors and substance dependence.

Acknowledgments

Margaret Devitt, Lisa Halberstadt, and Victor Robinson supervised data collection. We thank the members of the Laboratory for the Study of Substance Use and Psychopathology at the University of Southern California for their helpful feedback on this paper.

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