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Journal

Alcohol Clinical and Experimental Research, 38(1)

ISSN

0145-6008

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Publication Date

2014

DOI

10.1111/acer.12220

Peer reviewed

The Patterns of Drug and Alcohol Use and Associated Problems Over 30 Years in 397 Men

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Background: Alcohol and drug use disorders (AUDs and SUDs) and their combination are relatively common and often occur together. However, the relationships of potential early life correlates of alcohol and drug disorders to the combined diagnoses have rarely been evaluated in long-term prospective studies or in populations at high risk of one of these diagnoses but not the other.

Methods: Data were analyzed from 397 males (half with an alcohol-dependent father) who had no AUDs or SUDs at age 20 and who were followed approximately every 5 years for 3 decades. Early life correlates and the course of AUDs, SUDs, and combined disorders were evaluated for 4 groups of subjects based on subsequent alcohol and/or drug diagnoses.

Results: While the overall rates of the development of AUDs and SUDs were 41 and 21%, respectively, the rates of the second substance-related diagnosis were almost 2-fold higher for individuals who had the first condition. Among potential risk factors, scores for externalizing traits were elevated for men with AUDs, SUDs, and their combination, but a low level of response (low LR) to alcohol was associated only with the risk of AUDs, even when observed in the context of SUDs. The same earlier life characteristics that related to AUDs and to SUDs also related to the combination of these diagnoses in the same person. Finally, in this prospective study, subjects with both AUDs and SUDs had a more severe course than subjects with either condition alone.

Conclusions: This prospective evaluation of a group at high risk of AUDs confirmed the selective impact of the low LR on the risk of AUDs, the relationship of externalizing characteristics to both AUDs and SUDs and confirmed the more severe clinical course for both conditions when seen together.

Key Words: Alcoholism, Drug Dependence, Comorbidity, Level of Response to Alcohol, Externalizing Clinical Course.

THE USE OF alcohol and drugs, and associated life problems are common in the United States. Eighty percent of men and women have consumed alcohol, and almost half have taken an illicit drug (Substance Abuse and Mental Health Services Administration [SAMHSA], 2003). While most users do not develop repetitive problems, heavy intake of each substance carries risks of medical and psychiatric problems, and 5 to 20% of users across drug types develop an alcohol or substance use disorder (AUD or SUD; Kessler et al., 2005; Schuckit, 2006a; Teesson et al., 2010; Wagner and Anthony, 2002).

Some subgroups carry higher vulnerabilities to AUDs and/or SUDs. These include genetically influenced characteristics of impulsivity or sensation seeking (externalizing phenotypes) and anxiety or depressive symptoms (internalizing characteristics) that enhance the risk of both AUDs

and SUDs (Schuckit, 2009; Slutske et al., 2002; Yip et al., 2012). Additional preexisting phenotypes increase the risk of only AUDs, including how a person responds to alcohol (Newlin and Renton, 2010; Quinn and Fromme, 2011). The most widely studied alcohol response characteristic is a low level of response (low LR) to alcohol that reflects the need for a higher number of drinks to experience effects (Chung and Martin, 2009; Schuckit and Smith, 2011; Schuckit et al., 2011, 2012). Other characteristics with higher risks of substance-related problems include entering treatment for medical or psychiatric conditions, family histories (FHs) of alcohol and/or drug problems, and demographic variables such as Caucasian heritage (Compton et al., 2006; Fein and Landman, 2005; Wagner and Anthony, 2002; Wu et al., 2011).

The presence of either an AUD or SUD increases the probability that the other substance-related condition will develop (Goldstein et al., 2012; Stinson et al., 2005; Teesson et al., 2010). Comorbid SUDs and AUDs are associated with an earlier onset and greater number of problems for each disorder, lower life achievement, more medical and psychiatric problems, greater cognitive impairments, more violence, a greater likelihood of seeking treatment, and early death (Booth et al., 2010; Compton et al., 2003, 2006; Di Forti et al., 2012; Heil et al., 2001; Herrero et al., 2007; Moore et al., 2007; Neumark et al., 2000; Schuckit et al.,

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Received for publication February 26, 2013; accepted May 6, 2013.

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DOI: 10.1111/acer.12220

2013; Shaffer and Eber, 2002; Stenbacka et al., 2010; Teesson et al., 2010).

While the clinical implications of concomitant alcohol and drug problems are well established, few studies have prospectively evaluated how the correlates of AUDs and SUDs relate to combined diagnoses, and most focus on a limited number of earlier life characteristics. Cross-sectional and retrospective reports also make it difficult to disentangle whether the more severe clinical course (e.g., more intense substance use and related problems) for combined AUDs and SUDs is the consequence of concomitant substance-related syndromes or reflects a unique pattern of preexisting conditions that enhances both the risk of multiple types of substance problems and greater life impairment. No study has evaluated whether characteristics linked to combined substance-related conditions remain robust if the studied population is at high risk of one type of substance diagnosis (e.g., AUDs) but not the other (e.g., SUDs).

To help address these issues, we present data from a 30-year prospective study of a nonclinical and relatively high-functioning sample of 397 men to test 5 hypotheses: (1) the presence of either an AUD or an SUD will increase the risk of the other diagnosis; (2) earlier life externalizing and internalizing characteristics will relate to both future AUDs and SUDs; (3) a low LR to alcohol will predict AUDs but not SUDs; (4) the development of combined AUDs plus SUDs will be related to the combination of a low LR as well as externalizing and internalizing characteristics; and (5) the presence of AUDs and SUDs together will be associated with a greater intensity of use of substances and related problems for both conditions.

MATERIALS AND METHODS

Subjects (probands) for these analyses were 397 men who completed baseline (Time 1 or T1) evaluations and all follow-ups from approximate ages 20 to 50 in the San Diego Prospective Study (SDPS; Schuckit and Smith, 1996, 2011; Schuckit et al., 2013). These men represent 90.0% of 442 individuals who entered the study, were alive at the age 50 follow-up, and participated in all evaluations at 10 (T10), 15 (T15), 20 (T20), 25 (T25), and 30 (T30) years. At T1, these subjects responded to mailed questionnaires distributed annually between 1978 and 1988 to new groups of 18-to-25-year-old Caucasian (including White Hispanic) students and nonacademic staff at the University of California, San Diego, selecting those who indicated they had experience with alcohol but never developed an AUD or SUD. For the approximately 60% who responded, additional exclusion criteria included bipolar disorder, schizophrenia, or the report of physical problems that precluded alcohol challenges. The original protocol was limited to males to optimize the rate of expression of AUDs over time, and to Caucasians because few African-Americans attended UCSD and 40% of Asians had alcohol-related flushing that could affect their LR measures. The requirement that probands did not have an SUD or AUD excluded individuals with early onset substance-related disorders that often reflect preexisting severe conduct or antisocial problems (Schuckit, 2009; Slutske et al., 2002). Individuals were selected as matched pairs of sons of alcohol-dependent fathers and FH-negative controls who were similar on demography as well as alcohol and drug use histories. By T1, 64% of these probands had some experience with illicit substances.

Baseline data were gathered using a variation of the Renard Diagnostic Interview, and at follow-up using questions from the Semi-Structured Assessment for the Genetics of Alcoholism interview (Hesselbrock et al., 1999; Robins et al., 1981). The latter has 1-week retest reliabilities for SUDs and AUDs of approximately 0.75 (Hesselbrock et al., 1999). Follow-up information was gathered from subjects and resource persons (spouses or first-degree relatives) who gave information using an interview similar to the probands, with the higher figure for an item from either informant used if the 2 sources disagreed. Follow-up data included the prior 5-year interval use of alcohol, illicit drugs, and cigarettes, as well as personal and FHs of DSM-IV substance-related and independent major depressive and anxiety disorders (American Psychiatric Association, 1994). The Family History Assessment Module was used to gather information regarding lifetime AUDs and SUDs in the proband's biological parents (Rice et al., 1995).

As described in detail elsewhere, baseline LRs for probands were determined through alcohol-related changes in subjective feelings of intoxication, standing steadiness, and hormones (e.g., cortisol) at breath alcohol concentrations of approximately 60 mg/dl, as measured by an Intoximeter (Eng et al., 2005; Schuckit and Gold, 1988; Schuckit and Smith, 1996). Across multiple sessions, all subjects consumed 0.75 ml of alcohol or placebo and were evaluated over 3 hours as their blood alcohol concentrations (BACs) rose, peaked and decreased to close to zero. Z-scores were used to combine data into 1 overall LR score where lower values reflected lower LRs per drink. At T15, probands completed the Self-Report of the Effects of Alcohol (SRE) questionnaire regarding the number of drinks required for effects during 3 life epochs (the first 5 times of drinking [SRE5], the most recent 3 months, and their period of heaviest drinking). SRE5 and total scores incorporating all 3 epochs (SRET) were generated by summing the number of drinks required for up to 4 effects (feeling first effect, slurring speech, unsteady gait, or unwanted falling asleep), and dividing that by the number of the effects reported (Ray et al., 2007; Schuckit et al., 1997). Thus, higher SRE scores indicate more drinks needed for effects, or a lower LR per drink. The SRE Cronbach's α is >0.90, with retest reliabilities of 0.8. Externalizing characteristics were first evaluated at T10 and T15 using the novelty seeking from the Tridimensional Personality Questionnaire, Sensation Seeking from the Zuckerman Questionnaire, and Impulsivity from the Karolinska Personality Questionnaire (Cloninger et al., 1996; Schalling and Asberg, 1985; Zuckerman and Kuhlman, 2000).

To evaluate the hypotheses, emphasis was placed on LR, externalizing characteristics (e.g., novelty seeking, sensation seeking, and impulsivity) and internalizing items (likely to reflect seeking mental health help and depressive symptoms) along with the demographic and alcohol/drug variables likely to predict future alcohol and substance difficulties. Most analyses focused on 4 proband groups regarding substance-related diagnoses over the 30 years: (i) men who developed both SUDs and AUDs over the follow-up (Group 1); (ii) those with follow-up SUDs only (Group 2); (iii) subjects who developed AUDs only (Group 3); and (iv) individuals developing neither diagnosis during the 3 decades (Group 4). Comparisons regarding Hypotheses 2 to 4 used analysis of variance or chi-square across all 4 groups, with an emphasis on LR, externalizing, and internalizing characteristics along with demographic and earlier alcohol and drug use items. Significant differences were followed with a planned comparison to evaluate if the groups with AUD and/or SUD diagnoses differed from Group 4 with no diagnosis to identify relevant items to test regarding association with Groups 1, 2, and 3 separately. Those significant items were then entered into a series of backward elimination logistic regressions to evaluate if LR, externalizing, and/or internalizing items were still significantly related to each of the 3 groups with diagnoses when considered in the context of other significant items. Comparisons regarding Hypothesis 5 (relating to the severity of the clinical course of AUDs

and/or SUDs) were limited to Groups 1 to 3 who had relevant diagnoses, where an overall significant difference across groups was followed by planned comparisons of how Groups 2 and 3 differed from the combined diagnosis Group 1. For all evaluations, missing data were handled through a maximum likelihood procedure (Collins et al., 2001), including 6.8% who needed correction for 1 item and 0.8% for 2 items.

RESULTS

As demonstrated by the distribution of the 4 groups in Table 1, over the 30 years, 41.3% (Groups 1 plus 3) of the 397 men met criteria for an AUD, while 20.6% (Groups 1 plus 2) fulfilled criteria for an SUD. The SUDs included 51.2% of the 397 men with a cannabis use disorder only, 25.6% with an amphetamine and/or cocaine diagnosis only, 14.6% with combined cannabis and stimulant diagnoses, and 8.5% with an SUD related to cannabis or stimulants combined with other drug conditions. Consistent with Hypothesis 1 (the presence of one diagnosis will increase the risk of the other), in this prospective study of men at high risk of AUDs, the rate of a second substance-related diagnosis was almost 2-fold higher among individuals who had either SUDs or AUDs. Thus, 62 of the 164 (37.8%) probands with an AUD in Groups 1 plus 3 also had an SUD, and 62 of the 82 (75.6%) men with an SUD in Groups 1 plus 2 also had an AUD.

The 4 groups of subjects in Table 1 differed on a broad range of early life characteristics. The results indicated

significant differences for earlier life LR and externalizing characteristics, but not for having seen a mental health worker or reporting depressive syndromes (internalizing variables). There were also differences for several demographic, alcohol, and drug use items. All significant alcohol, drug, and externalizing items in that table also differentiated between the combined Groups 1 through 3 versus the no diagnosis Group 4.

In Table 2, further analyses were then carried out to more directly evaluate how items from Table 1 that were significantly different across the combined Groups 1 to 3 versus Group 4 performed when each of Groups 1, 2, and 3 was evaluated for differences from Group 4. This approach used a series of backward elimination logistic regressions to identify the odds ratios (ORs) for optimal combinations of items for each group that best differentiated it from the no diagnosis Group 4. In Table 2, the regression predicting Group 3 (AUDs only) from among Group 3 plus the no diagnosis Group 4 identified 6 items including: a lower LR per drink; a higher score on an externalizing questionnaire; 2 alcohol use characteristics; 1 drug use item; and lower T1 education. Five of these 6 items also related to the combined diagnosis Group 1 compared with Group 4, with the sixth characteristic similar to Group 3 in that it involved an externalizing questionnaire score. The regression relating to Group 2 (SUD only) from among Groups 2 plus 4 had contributions from 3 items: a higher score on an externalizing questionnaire, 1 alcohol, and 1 drug item (but not LR). All 3

Table 1. Demography at Baseline (T1) and Personality Test Scores for 397 Men Divided into Groups Based on Follow-Up Alcohol and Drug Diagnoses

Group number	1	2	3	4		Planned comparison
Group	SUD + AUD N = 62 (15.6%)	SUD N = 20 (5.0%)	AUD N = 102 (25.7%)	Neither N = 213 (53.6%)	F-test or χ^2	1-3 vs. 4
<i>T1 Characteristics</i>						
<i>Demography</i>						
Age (years)	22.6 (2.02)	23.4 (2.14)	22.7 (1.88)	23.3 (1.94)	3.47 ^a	
Race (% White)	98.4	95.0	98.0	95.8	1.89	
Education (years)	15.4 (1.37)	16.2 (1.50)	15.4 (1.28)	16.3 (1.64)	10.03 ^c	<0.001
Religion (%yes)	80.6	60.0	77.5	72.8	4.26	
Married (%yes)	14.5	15.0	12.7	22.5	5.38	
<i>Alcohol-related items</i>						
Alcohol challenge LR	-0.7 (0.64)	-0.4 (0.88)	-0.8 (0.78)	-0.3 (0.85)	9.45 ^c	0.001
Usual drinks/occasion (6 months)	3.5 (1.52)	2.8 (1.16)	3.4 (1.42)	2.4 (1.27)	19.43 ^c	<0.001
Usual frequency/mo (6 months)	10.9 (6.60)	11.6 (6.02)	9.7 (5.56)	7.2 (5.95)	9.86 ^c	<0.001
Number of alcohol problems ever	1.5 (1.52)	1.4 (1.39)	1.6 (1.51)	0.6 (0.91)	20.99 ^c	<0.001
Family history AUD (%)	71.0	50.0	59.8	48.8	10.82 ^a	0.01
<i>Drug-related items</i>						
Cannabis use (%yes)	75.8	65.0	70.6	56.3	10.99 ^a	0.001
Amphetamine use (%yes)	40.3	40.0	30.4	11.3	34.20 ^c	0.001
Number of drug problems	0.5 (0.76)	0.5 (0.69)	0.3 (0.78)	0.2 (0.54)	4.28 ^b	0.001
Family history SUD (%)	3.2	0.0	4.9	0.05	7.75 ^a	0.02
<i>Externalizing and internalizing</i>						
Mental health worker (%yes)	16.1	25.0	16.7	12.2	3.18	
Ever depressed (%yes)	14.5	10.0	7.8	14.1	2.88	
TPQ novelty seeking	16.8 (4.80)	17.2 (5.01)	17.1 (4.89)	14.5 (4.36)	10.04 ^c	<0.001
Zuckerman sensation seeking	22.2 (5.29)	22.5 (4.17)	21.6 (4.85)	18.5 (5.49)	13.80 ^c	<0.001
Karolinska impulsivity	48.5 (5.10)	46.0 (4.67)	47.4 (5.07)	45.1 (5.48)	8.58 ^c	<0.001

SUD, substance use disorder (abuse or dependence on an illicit drug); AUD, alcohol use disorder (abuse or dependence on alcohol); LR, level of response to alcohol from an alcohol challenge; TPQ, Tridimensional Personality Questionnaire.

^a $p < 0.05$, ^b $p < 0.01$, ^c $p < 0.001$.

Table 2. Odds Ratios from Backward Elimination Logistic Regressions Comparing Group 1, 2, and 3 Separately with Group 4 Using Items Significantly Related to Group 1 Through 3 Membership in the Planned Comparisons Table 1

	Group 1 (SUD + AUD) vs. 4 (neither SUD or AUD)	Group 2 (SUD only) vs. 4	Group 3 (AUD only) vs. 4
Demography			
Education (years)	0.74		0.74
Alcohol-related items			
Alcohol challenge LR	0.59		0.50
Usual drinks/occasion (6 months)	1.35		1.26
Usual freq/mo (6 months)	1.08		
Number of alcohol problems ever	1.52	1.74	1.78
Family history AUD (%)	2.42		
Drug-related items			
Cannabinol use (%yes)			
Amphetamine use (%yes)	3.15	2.76*	2.32
Number of drug problems			
Family history SUD (%)			
Externalizing			
TPQ novelty seeking			1.12
Zuckerman sensation seeking		1.14	
Karolinska impulsivity	1.10		

* $p = 0.065$.

The definitions of LR, SUD, AUD, and TPQ are defined in Table 1.

types of items also related to Group 1 membership, but with a different externalizing questionnaire score. Thus, 5 of the 8 items that contributed to the regression for Group 1 versus Group 4, also related to Group 2 and/or Group 3, with 1 of the additional items relating to an externalizing score from a different questionnaire. Similar results for these 3 regressions were seen if hierarchical logistic regressions were used focusing on blocks of demographic items, alcohol, and drug use items, and then LR and externalizing items, with the exception that the equation relating to the block of externalizing characteristics and LR regarding the small Group 2 was a trend ($p = 0.081$).

In summary regarding Hypotheses 2 to 4 (externalizing and internalizing characteristics will relate to both AUDs and SUDs, LR will relate to AUDs only, and the combined diagnosis will relate to the same items that predict the 2 substance diagnoses alone), externalizing characteristics related to all 3 diagnostic groups, while LR related only to groups with later AUDs. Overall, the characteristics that related to AUDs alone combined with those that best identified subjects with SUDs alone were associated with the combined diagnoses in Group 1, with few predictors that were uniquely related to Group 1.

Table 3 addresses Hypothesis 5 (more intense alcohol and drug use and problems will be observed when AUDs and SUDs are seen in the same person). Here, planned comparisons were used because some items were only relevant to

groups with AUDs (e.g., age of onset of the AUD) and some were only appropriate for probands with SUDs. Beginning with demography, the only overall significant difference across the 3 groups at age 50 was the higher proportion of individuals in Group 3 (AUD only) who had ever been married, a finding that reflected higher proportions in Group 3 versus the comorbid diagnosis Group 1. The course of alcohol-related items for the 2 AUD groups (1 and 3) indicated that members of the combined diagnosis Group 1 endorsed more AUD items, an earlier AUD onset, a higher risk of alcohol-induced mood disorders, and a greater proportion who received formal AUD treatment or who attended Alcoholics Anonymous meetings compared with Group 3. The drug-related items for the 2 SUD groups (1 and 2) indicated that members of Group 1 were more likely to use tobacco and reported a higher number of SUD items. Mental health histories over the 30 years were generally similar across the 3 groups, except for a greater probability of having seen a mental health worker for the combined diagnosis Group 1 compared with the AUD diagnostic Group 3.

The demographic (ever married) and alcohol-related characteristics in Table 3 that differentiated between the AUD Groups 1 and 3 were likely to be correlated, so these 6 items were entered into a backward elimination logistic regression analysis to determine which variables remained significantly related to a combined AUD plus SUD outcome (Group 1) among individuals in Groups 1 plus 3. The results demonstrated significant ORs for Group 1 membership for the number of AUD items endorsed (OR 1.20), an alcohol-induced mood diagnosis (OR 6.76), and having received formal AUD treatment (OR 3.89). The 2 drug-related items and the SRET score that differentiated between Group 1 and Group 2 in Table 3 were entered into a logistic regression predicting Group 1 membership from among Groups 1 plus 2, with only the SRET contributing significantly (OR 2.12). If SRET was removed from the equation, approximately equal contributions were seen from use of tobacco products and the number of SUD items.

DISCUSSION

These analyses evaluated whether a long-term prospective study of the development of AUDs and/or SUDs in men corroborated several findings from prior cross-sectional and retrospective studies. The rates of alcohol-related conditions in the current sample reflect the fact that half of the men had an alcoholic parent. Over the 30 years, 41% of these probands developed an AUD, compared with an estimated 12 month or lifetime risk of 15 to 20% in the general population (e.g., Chou et al., 2012; Kessler et al., 2005; Teesson et al., 2010). However, considering the fact that these high-functioning probands had not been selected for an FH of SUDs, the 21% rate of drug-related conditions found in these analyses, compared with general population lifetime estimates of about 10% (Anthony et al., 2005; Kessler et al., 2005; Wagner and Anthony, 2002), might have been less expected.

Table 3. Alcohol, Drug, Mental Health Histories Over the 30 Years of Follow-Up for Men with Follow-Up SUD and/or AUD Diagnosis

Group number	1	2	3		Planned comparisons	
Group	SUD + AUD N = 62 (15.6%)	SUD N = 20 (5.0%)	AUD N = 102 (25.7%)	F-test or χ^2	1 vs. 2	1 vs. 3
Demography at T30						
Education (years)	17.2 (2.15)	17.5 (1.82)	17.4 (2.33)	0.16		
High-status job (%)	59.7	75.0	57.9	2.07		
Ever married (%)	79.0	75.0	92.2	7.66 ^a		0.02
Ever divorced (%)	32.3	15.0	31.4	2.39		
Alcohol-related items						
SRE5	3.3 (1.07)	3.3 (1.39)	3.5 (1.38)	0.44		
SRET	4.8 (1.55)	3.6 (1.17)	4.4 (1.28)	6.23 ^b	0.001	
Usual drinks/occasion	3.1 (1.53)	2.1 (0.53)	2.9 (0.95)	6.56 ^b	<0.001	
Usual freq/mo	14.7 (7.76)	14.7 (7.56)	15.4 (6.45)	0.25		
Maximum drinks	19.3 (7.12)	12.6 (4.77)	17.6 (7.96)	6.12 ^b	0.001	
Number of AUD items	4.9 (2.23)	1.1 (0.79)	3.7 (2.00)	28.10 ^c	<0.001	<0.001
Age onset of AUD	27.5 (6.59)	NA	31.0 (8.82)	7.60 ^b		0.01
Alcohol-induced mood Dx (%)	14.5	NA	2.0	9.71 ^b		0.01
Formal AUD Rx (%)	24.2	NA	3.9	15.47 ^c		<0.001
AA participation (%)	32.3	NA	11.8	10.31 ^c		0.001
AUD at T30 (%)	58.1	NA	58.4	0.01		
Drug-related items						
Substance use (% yes)	100.0	100.0	83.3	15.06 ^c		0.001
Cannabinol use (% yes)	98.4	100.0	78.4	17.25 ^c		<0.001
Stimulant use (% yes)	83.9	70.0	36.3	37.24 ^c		<0.001
Other drugs (% yes)	77.4	90.0	35.3	38.55 ^c		<0.001
Tobacco (% yes)	69.4	45.0	57.8	4.34	0.05	
Age onset of SUDs	28.0 (7.10)	29.0 (5.69)	NA	0.34		
Substance-induced disorder (%)	11.3	0.0	NA	2.50		
Number of SUDs	1.3 (0.48)	1.2 (0.41)	NA	0.24		
Number of SUD items	5.0 (2.52)	3.8 (1.44)	0.2 (0.39)	195.05 ^c	0.004	<0.001
Cannabinol Dx (%)	66.1	70.0	NA	0.10		
Stimulant Dx (%)	50.0	40.0	NA	0.61		
Other drug Dx (%)	6.5	10.0	NA	0.28		
SUD at T30 (%)	29.0	20.0	NA	0.63		
Internalizing						
See mental health worker	58.1	45.0	42.2	3.98		<0.05
Independent mood Dx	14.5	15.0	10.8	0.62		
Prescribed antidepressants	16.1	10.0	9.8	1.55		

The definitions of SUD and AUD are defined as in Table 1; High-status job = MD, PHD, JD, or owner of large business. SRE, the self-report measure of the number of drinks needed for effects the first 5 times of drinking (SRE5) or over 3 life epochs (SRET); Dx, diagnosis; Rx, treatment; AA, Alcoholics Anonymous.

^a $p < 0.05$, ^b $p < 0.01$, ^c $p < 0.001$.

As predicted by Hypothesis 1 and several reports in the literature (e.g., Stinson et al., 2005; Teesson et al., 2010), the presence of either an AUD or an SUD was associated with an increased rate of the other diagnosis. This increase for SUDs among subjects with AUDs was in the range of individuals with alcohol abuse who developed an SUD as reported in an earlier study (Goldstein et al., 2012), although not as great an increase in SUDs evidenced in subjects with alcohol dependence in that investigation. The less robust increase in this study compared with some prior reports may reflect the exclusion from the protocol of subjects with severe antisocial problems, the few subjects with an FH of SUDs, and the overall high functioning of these probands.

The general similarity among the probands regarding baseline demography and psychiatric histories facilitated our ability to focus on the impact of several genetically influenced intermediate phenotypes that relate to the risk of SUDs and/or AUDs (Schuckit, 2009). Regarding Hypothesis 2 (externalizing and internalizing characteristics will predict

both AUDs and SUDs), in Tables 1 and 2, while the 4 outcome groups did not differ greatly on internalizing problems, higher scores on externalizing traits were related to SUDs, AUDs, and combined diagnoses. The fact that the externalizing questionnaires had not been measured at T1, but were evaluated at T10 or T15, means that we can only describe associations of these scores with the 4 outcomes, although the trait nature of the measures implies a possible causal relationship.

Regarding Hypothesis 3 (a low LR will predict AUDs but not SUDs), the first 2 tables also demonstrated a consistent relationship between a baseline low LR with the risk of AUDs, but LR was not related to the vulnerability toward SUDs. These findings underscore the heterogeneity among genetically influenced characteristics that impact on the risk of AUDs and/or SUDs. The results are consistent with the literature indicating that some intermediate phenotypes (e.g., externalizing characteristics) relate to both AUD and SUD development (Schuckit, 2009; Slutske et al., 2002), while

other characteristics, such as the low LR to alcohol and the skin flush associated with drinking, have been reported to be associated with the risk of AUDs alone (Eng et al., 2007; Schuckit, 2009; Schuckit and Smith, 1996, 2011).

Regarding Hypothesis 4 (combined diagnoses will relate to the items that predict AUDs plus those that predict SUDs), there were few unique earlier life correlates of combined diagnoses, and the predictors of Group 1 reflected items that related to AUDs alone and SUDs alone. One important caveat regarding this conclusion, however, relates to the differences across Groups 1, 2, and 3 regarding the performance of novelty seeking, sensation seeking, and impulsivity, as these externalizing characteristics are not homogenous (Courtney et al., 2012). Additional study is needed to explore the possibility that the different scores on these questionnaires across Groups 1 to 3 may have clinically relevant implications.

The data in Table 3 support Hypothesis 5 (combined diagnoses will be associated with more alcohol and drug use and problems than will be seen with either AUDs or SUDs alone). Even in this prospective study of men at high risk of AUDs, the development of combined AUDs and SUDs was associated with heavier substance use and more alcohol and drug problems over the 30 years for men in Group 1 compared with Groups 2 or 3. This result was observed despite similar ages, racial distributions, education, religious involvement, as well as alcohol and drug histories at T1 for Groups 1 and 3. The course of combined diagnoses might reflect the impact of concomitant substance use itself, perhaps through greater impaired judgment, poor executive functioning, and problems in mood regulation associated with the exposure to multiple types of substances (Casper et al., 2010; Tait et al., 2011).

Table 3 also offers information regarding the outcomes at T30 for SUDs and AUDs in these high-functioning men from a nonclinical population. As described in a recent article (Trim et al., 2013), 42% of these probands with AUDs no longer met criteria for alcohol abuse or dependence in the approximate 5 years prior to T30. It is interesting to note that those results were seen for members of both Group 1 and Group 3. Remissions at T30 were even more striking for SUDs where >70% of Group 1 and 2 men no longer fulfilled criteria for these diagnoses, with similar rates for the combined diagnosis Group 1 and the SUD only Group 2. These impressive rates of recovery may reflect the combination of indicators of a good prognosis in these subjects regarding their nonclinical status at T1, the high proportion who were married during the follow-up, their high education level, and the general absence of premorbid conduct or antisocial problems, as well as the high rates of spontaneous recovery associated with substance-related conditions over time (Dawson et al., 2006; Schuckit, 2006a). Results might be different in less educated or more antisocial groups recruited from clinical populations (Boschloo et al., 2012).

Several caveats must be kept in mind when viewing these findings. On the positive side, the SDPS is a large study with intensive follow-up interviews carried out about every

5 years over 30 years. The project was structured to allow for evaluation of the development of AUDs and related problems over time in individuals for whom the impact of several additional factors that affect the risk of alcoholism was partially controlled. Thus, the probands did not have severe conduct problems or prior histories of bipolar disorder or schizophrenia, each of which enhance the risk of all substance-related disorders (Schuckit, 2006a,b; Yip et al., 2012). Those steps were taken to optimize the ability to evaluate the relationship between the low LR to alcohol and the future development of AUDs. These deliberate exclusions were also likely to have contributed to selecting probands with future high levels of functioning despite their elevated risk of AUDs. However, those steps and the relative homogeneity of the sample regarding sex, education, and race potentially limited the generalizability of the findings. An additional caveat is that, while the population was relatively large for a long-term intensive follow-up, the number of individuals developing SUDs was relatively small with resulting limited statistical power in some analyses. This contributed to the decision to combine abuse and dependence into a single category and to consider amphetamines and cocaine as stimulants. It is also important to emphasize that while the results regarding externalizing personality test scores were consistent with the predicted direction of such values, only 3 questionnaires were used and those were measured at least 10 years after subjects entered the protocol. In addition, earlier life internalizing phenomena were evaluated by only baseline histories of depressions or mental health treatment. Finally, the approach to regressions used here may have optimized statistical power by minimizing standard errors and producing relatively narrow confidence intervals, although an alternate method, hierarchical logistic regression, produced similar results but has the limitation of not requiring that every item in the block add significantly to the prediction.

ACKNOWLEDGMENT

This study was supported by NIH/NIAAA grant 2R01AA05526.

REFERENCES

- American Psychiatric Association (1994) *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. American Psychiatric Press, Washington DC.
- Anthony JC, Chen CY, Storr CL (2005) Drug dependence epidemiology. *Clin Neurosci Res* 5:55–68.
- Booth BM, Curran G, Han X, Wright P, Frith S, Leukefeld C, Falck R, Carlson RG (2010) Longitudinal relationship between psychological distress and multiple substance use: results from a three-year multisite natural-history study of rural stimulant users. *J Stud Alcohol Drugs* 71: 258–267.
- Boschloo L, Vogelzangs N, van den Brink W, Smit JH, Beekman AT, Penninx BW (2012) Predictors of the 2-year recurrence and persistence of alcohol dependence. *Addiction* 107:1590–1598.
- Casper K, Arndt S, Yucuis R, McKirgan L, Spinks R (2010) Effects of alcohol- and cigarette-use disorders on global and specific measures of cognition in middle-age adults. *J Stud Alcohol Drugs* 71:192–200.

- Chou SP, Lee HK, Cho MJ, Park J-I, Dawson DA, Grant BF (2012) Alcohol use disorders, nicotine dependence, and co-occurring mood and anxiety disorders in the United States and South Korea—a cross-national comparison. *Alcohol Clin Exp Res* 36:654–662.
- Chung T, Martin CS (2009) Subjective stimulant and sedative effects of alcohol during early drinking experiences predict alcohol involvement in treated adolescents. *J Stud Alcohol Drugs* 70:660–667.
- Cloninger CR, Adolfsson R, Svrakic NM (1996) Mapping genes for human personality. *Nat Genet* 12:3–4.
- Collins LM, Schafer JL, Kam CM (2001) A comparison of inclusive and restrictive strategies in modern missing data procedures. *Psychol Methods* 6:330–351.
- Compton WM, Conway KP, Stinson FS, Grant BF (2006) Changes in the prevalence of major depression and comorbid substance use disorders in the United States between 1991–1992 and 2001–2002. *Am J Psychiatry* 163:2141–2147.
- Compton WM III, Cottler LB, Jacobs JL, Ben-Abdallah A, Spitznagel EL (2003) The role of psychiatric disorders in predicting drug dependence treatment outcomes. *Am J Psychiatry* 160:890–895.
- Courtney KE, Arellano R, Levenson EB, Galvan A, Poldrack RA (2012) The relationship between measures of impulsivity and alcohol misuse: an integrative structural equation and modeling approach. *Alcohol Clin Exp Res* 36:923–931.
- Dawson DA, Grant BF, Stinson FS, Chou PS (2006) Maturing out of alcohol dependence: the impact of transitional life events. *J Stud Alcohol Drugs* 67:195–203.
- Di Forti M, Lyegbe C, Sallis H, Kolliakou A, Falcone MA, Paparelli A, Sirianni M, La Cascia C, Stilo SA, Marques TR, Handley R, Mondelli V, Dazzan P, Pariante C, David AS, Morgan C, Powell J, Murray RM (2012) Confirmation that the AKT1 (rs2494732) genotype influences the risk of psychosis in cannabis users. *Biol Psychiatry* 72:811–816.
- Eng MY, Luczak SE, Wall TL (2007) ALDH2, ADH1B, and ADH1C genotypes in Asians: a literature review. *Alcohol Res Health* 30:22–27.
- Eng MY, Schuckit MA, Smith TL (2005) The level of response to alcohol in daughters of alcoholics and controls. *Drug Alcohol Depend* 79:83–93.
- Fein G, Landman B (2005) Treated and treatment-naïve alcoholics come from different populations. *Alcohol Clin Exp Res* 35:19–26.
- Goldstein RB, Dawson DA, Chou SP (2012) Sex differences in prevalence and comorbidity of alcohol and drug use disorders: results from wave 2 of the national Epidemiologic Survey on Alcohol and Related Conditions. *J Stud Alcohol Drugs* 73:938–950.
- Heil SH, Badger GJ, Higgins ST (2001) Alcohol dependence among cocaine-dependent outpatients: demographics, drug use, treatment outcome and other characteristics. *J Stud Alcohol* 62:14–22.
- Herrero MJ, Domingo-Salvany A, Torrens M, Brugal MT, Itinere Investigators (2007) Psychiatric comorbidity in young cocaine users: induced versus independent disorders. *Addiction* 103:284–293.
- Hesselbrock MN, Easton C, Bucholz KK, Schuckit M, Hesselbrock V (1999) A validity study of the SSAGA—a comparison with the SCAN. *Addiction* 94:1361–1370.
- Kessler RC, Berglund P, Demler O, Jin R, Walters EE (2005) Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry* 62:593–602.
- Moore THM, Zammit S, Lingford-Hughes A, Barnes TRE, Jones PB, Burke M, Lewis G (2007) Cannabis use and risk of psychotic or affective mental health outcomes: a systemic review. *Lancet* 370:319–328.
- Neumark YD, Van Etten ML, Anthony JC (2000) “Drug dependence” and death: survival analysis of the Baltimore ECA sample from 1981 to 1995. *Subst Use Misuse* 35:313–327.
- Newlin DB, Renton RM (2010) High risk groups often have higher levels of alcohol response than low risk: the other side of the coin. *Alcohol Clin Exp Res* 34:199–202.
- Quinn PD, Fromme K (2011) Subjective response to alcohol challenge: a quantitative review. *Alcohol Clin Exp Res* 35:1759–1770.
- Ray LA, Audette A, DiCristoforo S, Odell K, Kaiser A, Hutchison KE (2007) Behavioral, laboratory, and genetic correlates of low level of response to alcohol. *Alcohol Clin Exp Res* 31:1–5.
- Rice JP, Reich T, Bucholz KK, Neuman RJ, Fishman R, Rochberg N, Hesselbrock VM, Nurnberger JI Jr, Schuckit MA, Begleiter H (1995) Comparison of direct interview and family history diagnoses of alcohol dependence. *Alcohol Clin Exp Res* 19:1018–1023.
- Robins LN, Helzer JE, Croughan J, Ratcliff KS (1981) National Institute of Mental Health Diagnostic Interview Schedule. Its history, characteristics, and validity. *Arch Gen Psychiatry* 38:381–389.
- Schalling D, Asberg M (1985) Biological and psychological correlates of impulsiveness and monotony in avoidance, in *The Biological Bases of Personality and Behavior, Vol. 1: Theories, Measurement Techniques, and Development* (Strelau J, Farley FJ, Gale A eds), pp 181–194. Hemisphere Publishing Corp/Harper & Row Publishers, New York.
- Schuckit MA (2006a) Drug and Alcohol Abuse: A Clinical Guide to Diagnosis and Treatment. 6th ed. Springer Science + Business Media, Inc., New York.
- Schuckit MA (2006b) Comorbidity between substance use and psychiatric conditions. *Addiction* 101(Suppl. 1):76–88.
- Schuckit MA (2009) An overview of genetic influences in alcoholism. *J Subst Abuse Treat* 36:5–14.
- Schuckit MA, Gold EO (1988) A simultaneous evaluation of multiple markers of ethanol/placebo challenges in sons of alcoholics and controls. *Arch Gen Psychiatry* 45:211–216.
- Schuckit MA, Kalmijn JA, Smith TL, Saunders G, Fromme K (2012) Structuring a college alcohol prevention program on the low level of response to alcohol model: a pilot study. *Alcohol Clin Exp Res* 36:1244–1252.
- Schuckit MA, Smith TL (1996) An 8-year follow-up of 450 sons of alcoholic and control subjects. *Arch Gen Psychiatry* 53:202–210.
- Schuckit MA, Smith TL (2011) Onset and course of alcoholism over 25 years in middle class men. *Drug Alcohol Depend* 113:21–28.
- Schuckit MA, Smith TL, Heron J, Hickman M, Macleod J, Lewis G, Davis JM, Hibbeln JR, Brown S, Zuccolo L, Miller LL, Davey-Smith G (2011) Testing a level of response to alcohol-based model of heavy drinking and alcohol problems in 1,905 17-year-olds. *Alcohol Clin Exp Res* 35:1897–1904.
- Schuckit MA, Smith TL, Kalmijn J (2013) Relationships among independent major depressions, alcohol and other substance use and related problems over 30 years in 397 families. *J Stud Alcohol Drugs* 74:271–279.
- Schuckit MA, Tipp JE, Smith TL, Wiesbeck GA, Kalmijn J (1997) The relationship between self-rating of the effects of alcohol and alcohol challenge results in ninety-eight young men. *J Stud Alcohol* 58:397–404.
- Shaffer HJ, Eber GB (2002) Temporal progression of cocaine dependence symptoms in the US National Comorbidity Survey. *Addiction* 97:543–554.
- Slutske WS, Heath AC, Madden PA, Bucholz KK, Statham DJ, Martin NG (2002) Personality and the genetic risk for alcohol dependence. *J Abnorm Psychol* 111:124–133.
- Stenbacka M, Leifman A, Romelsjö A (2010) Mortality and cause of death among 1705 illicit drug users: a 37-year follow up. *Drug Alcohol Rev* 29:21–27.
- Stinson FS, Grant BF, Dawson DA, Ruan WJ, Huang B, Saha T (2005) Comorbidity between DSM-IV alcohol and specific drug use disorders in the United States: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Drug Alcohol Depend* 80:105–116.
- Substance Abuse and Mental Health Services Administration [SAMHSA] (2003) Overview of Findings from the 2002 National Survey on Drug Use and Health. Office of Applied Studies, NHSDA Series H-21, DHHS Publication No. SMA 03-3774, Rockville, MD.
- Tait RJ, Mackinnon A, Christensen H (2011) Cannabis use and cognitive function: 8-year trajectory in a young adult cohort. *Addiction* 106:2195–2203.
- Teesson M, Hall W, Slade T, Mills K, Grove R, Mewton L, Baillie A, Haber P (2010) Prevalence and correlates of DSM-IV alcohol abuse and depen-

- dence in Australia: findings of the 2007 National Survey of Mental Health and Wellbeing. *Addiction* 105:2085–2094.
- Trim RS, Schuckit MA, Smith TL (2013) Predictors of initial and sustained remission from alcohol use disorders: findings from the 30-year follow-up of the San Diego Prospective Study. *Alcohol Clin Exp Res* doi: 10.1111/acer.12107 [Epub ahead of print].
- Wagner FA, Anthony JC (2002) From first drug use to drug dependence: developmental periods of risk for dependence upon marijuana, cocaine, and alcohol. *Neuropsychopharmacology* 26:479–488.
- Wu L-T, Woody GE, Yang C, Pan J-J, Blazer DG (2011) Racial/ethnic variations in substance-related disorders among adolescents in the United States. *Arch Gen Psychiatry* 68:1176–1185.
- Yip SW, Doherty J, Wakeley J, Saunders K, Tzagarakis C, de Wit H, Goodwin GM, Rogers RD (2012) Reduced subjective response to acute alcohol administration among young men with a broad bipolar phenotype. *Neuropsychopharmacology* 37:1808–1815.
- Zuckerman M, Kuhlman DM (2000) Personality and risk-taking: common biosocial factors. *J Pers* 68:999–1029.