A Comparison of Factors Associated With Substance-Induced Versus Independent Depressions*

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ABSTRACT. Objective: This article expands on the results from a 1997 report from the Collaborative Study on the Genetics of Alcoholism (COGA), using a new phase of the protocol to evaluate the prevalence and characteristics of substance-induced and independent major depressive episodes (MDEs) in a population of alcoholics and nonalcoholics. **Method:** Data were evaluated from Phase II of the six-center-wide COGA investigation using information gathered beginning in January 1997. Data were generated through face-to-face evaluations using the updated version of the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA-II) interview, with distinctions between substance-induced and independent MDEs based on the chronology of development of full depressive syndromes. The analyses focused on the 2,548 men and women who were divided into 351 individuals who had only an independent MDE (Group 1), 238 subjects who experienced only substance-induced MDEs, and 1,959 individuals with no MDE history. **Results:** The two MDE groups were similar in age, marital status, and religion; but those with substance-induced depressions (Group 2) were more likely to be original alcoholic probands, be males, be nonwhite, and have less education. They were also more likely to have alcohol, drug, or antisocial personality diagnoses and to report higher maximum drinks. In addition, only Group 2 subjects reported an elevated family history of alcohol diagnoses compared with the nondepressed Group 3. Subjects with independent MDEs were different from the comparison Group 3 regarding the family histories of independent MDEs. However, symptoms during the worst depressive episode were quite similar across Groups 1 and 2. **Conclusions:** This study corroborates a high rate of substance-induced MDEs among alcoholics, with these disorders explaining about half of the lifetime depressive episodes. The results also support the validity of the distinction between substance-induced and independent depressions regarding external validators of gender, substance-use patterns, and family histories of independent MDEs. (*J. Stud. Alcohol Drugs* **68:** 805-812, 2007)

THE ALCOHOL-USE DISORDERS (AUDs) and substance-use disorders (SUDs) of abuse and dependence are often accompanied by symptoms of additional psychiatric syndromes. This is especially true regarding psychotic symptoms among stimulant-dependent individuals and depressive syndromes in alcoholics (Altamura et al., 1990; Brown et al., 1995; Hasin et al., 2002; Nurnberger et al., 2004). In some cases, an independent psychiatric condition (i.e., a disorder that is not only seen temporarily in the context of alcohol or relevant drug intoxication or withdrawal) may have contributed to the risk for substance-use patterns, as can be seen with antisocial personality disorder (ASPD), schizophrenia, and manic depressive disease (Kessler et al., 1997; Slutske et al., 1998; Winokur et al., 1996). In these instances, as described in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR; American Psychiatric Association, 2000), the independent psychiatric disorders (e.g., ASPD, schizophrenia, or manic depressive disease) can usually be observed before the onset of abuse or dependence on a relevant substance and/or remain manifest after extended periods of abstinence. Optimal treatment for these independent psychiatric conditions requires appropriate interventions to address the psychiatric disorder, as well as steps to help individuals abstain from alcohol and illicit drugs to optimize their response to treatments for their psychiatric syndrome.

Intoxication or withdrawal associated with many of the substances of abuse (including alcohol) can also produce temporary substance-induced psychiatric conditions that closely resemble independent psychiatric syndromes. This makes substance use an important part of the differential diagnosis in evaluating patients with these psychiatric conditions (Schuckit, 2006). For example, temporary, but intense, depressions can be induced in research subjects consuming up to 20 drinks per day (Isbell et al., 1955; Tamerin et al., 1970) and are seen in a third or more of

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treatment-seeking, alcohol-dependent patients (Gilder et al., 2004; Schuckit et al., 1997). However, about half of these depressions developed only in the context of heavy drinking and markedly improved within 2-4 weeks of abstinence (Brown et al., 1995; Davidson, 1995; Kiefer and Barocka, 1999; Willenbring, 1986). Such substance-induced changes in mood may explain a substantial proportion of the major depressive episodes (MDEs) observed among alcoholics, and once these are considered, the rate of independent depressions may not be much higher among alcoholics than in the general population.

Regarding the general MDE risk, the National Comorbidity Survey and other studies reported a lifetime prevalence of MDEs of 13% to 16% in the United States, with prior year rates of 5% to 9% (Hasin et al., 2005; Kessler et al., 1994). Hasin et al. (2002) reported a 14.8% lifetime risk for independent depressions among patients dependent on cocaine, heroin, and/or alcohol (a number similar to the general population rates), along with a 20% rate for substance-induced depressions. Data from the first phase of the Collaborative Study on the Genetics of Alcoholism (COGA; Schuckit et al., 1997) indicated a lifetime rate for independent MDEs among alcoholics of 15.2% (also a number similar to the general population), with an additional 26.4% reporting substance-induced MDEs. Although the COGA data focused on lifetime risk, a 12-month prospective evaluation of treated alcoholics (Schuckit et al., 1994) reported a 1-year incidence of independent MDEs of 6.3%, a number also similar to the general population rates of 6.7% reported by Kessler et al. (2005) and 5.3% noted by Hasin et al. (2002). However, a retrospective 12-month prevalence of MDEs in the general population (about 95% of whom did not have an AUD or SUD) reported that, although 7.2% of the subjects had an MDE in the prior year, only 0.11% of the general population ever had a substance-induced MDE (Grant et al., 2004). The 12-month prevalence of an SUD was 4.1%, including 3.8% for alcohol dependence. If all the substance-induced conditions were found in this 4.1% of the population, their 1-year prevalence of substance-induced depressions may have been approximately 30%, a substantial proportion of the MDEs observed in this subgroup.

In Phase I of the COGA study, the potential clinical importance of substance-induced MDEs among alcoholics was supported by external validators, in which only alcoholic subjects with independent major depressions, but not those with substance-induced conditions, were more likely to have characteristics associated with independent MDEs (Schuckit et al., 1997). These factors included being female (odds ratio [OR] = 2.0), white (OR = 2.1), and having a first-degree relative with independent mania or major depressions (OR = 1.3-2.0) (Schuckit et al., 1997). In contrast, substance-induced disorders were predicted primarily by factors that might indicate more severe alcohol and drug dependence. However, the original COGA data were gathered in the early to mid-1990s, and no large investigation has attempted to corroborate those findings among large groups of alcoholics and comparison subjects. Furthermore, the 1997 study limited the data to alcohol-dependent individuals, and it is unclear whether similar distinctions between independent and induced disorders would have been observed among nonalcoholics. Therefore, the current analyses used a new phase of the COGA protocol to determine if similar results were generated from a new interview and new phase of the study using a data set incorporating both alcoholic and nonalcoholic subjects, including subjects from comparison families.

Method

The results presented here were generated using informed consent procedures to evaluate data from the Phase II evaluations from the six-center-wide COGA study (Bucholz et al., 1994; Schuckit et al., 1997). The original index subjects (or probands) were recruited from alcoholic patients who entered AUD or SUD treatment and met the DSM-III-R criteria for alcohol dependence, along with Feighner alcoholism (American Psychiatric Association, 1987; Feighner et al., 1972). These probands were selected if they had multiple alcoholic relatives, spoke English, did not have a life-threatening medical condition, and were not heavy intravenous drug users, without restrictions based on additional psychiatric diagnoses. Subsequently, all appropriate relatives of the COGA probands were invited to participate. Each center also identified a comparison group through random mailings to students at a university, driver's license records, or attendance records from medical and dental clinics, and were selected regardless of the presence or absence of alcohol or drug diagnoses. All available original probands and comparison individuals participated in multiple evaluations, including face-to-face interviews with the original Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA-I) instrument (Bucholz et al., 1994; Hesselbrock et al., 1999).

In the Phase II follow-up and family extension phase of the protocol, all relevant probands, comparison subjects, and relatives were asked to participate in interviews with the revised SSAGA interview (SSAGA-II). Compared with the initial SSAGA, this instrument focused on DSM-IV and covered several additional diagnoses. In the current analyses, subjects were placed into diagnostic categories using the DSM-IV criteria for MDEs (i.e., 2 weeks or more of daily depressed mood) and for abuse or dependence on alcohol or illicit drugs. Because family history was a variable of interest, all selected subjects were required to have at least one personally interviewed parent.

Subjects who were at least 18 years old and had ever experienced a DSM-IV MDE were further evaluated to

distinguish between substance-induced and independent depressions using the algorithm described in the earlier COGA article (Schuckit et al., 1997). First, a history of independent MDEs was determined by documenting if they ever had such an episode outside of the context of abuse or dependence on alcohol or relevant illicit substances, and if subjects ever had recent significant losses (i.e., grief) or illnesses or took medications that might produce an MDE-like syndrome. In this step, the rate of independent MDEs might have been exaggerated because some substance-induced conditions could have developed during heavy substance use shy of abuse or dependence. Subjects who denied histories consistent with independent MDEs were then evaluated to determine if such MDEs ever developed in the context of abuse or dependence on substances of abuse (especially alcohol), requiring that the full DSM-IV MDE criteria be fulfilled. Unfortunately, when a subject reported an independent MDE, no further systematic data were gathered regarding additional possible substance-induced depressions.

In the SSAGA, a standard drink was defined as the equivalent of 10-12 g of ethanol as consumed in 12 oz of beer, 5 oz of nonfortified wine, or a single shot (1.5 oz) of 80-proof distilled spirits. Individuals were considered smokers if they reported ever having consumed 10 or more cigarettes a day, and family histories of AUDs and independent major depressions were evaluated based on reports from personally interviewed biological mothers and fathers using DSM-IV criteria.

As described further in the following, subjects were placed into three mutually exclusive categories based on their personal MDE histories, with comparisons across groups using chi-square for categorical data and analysis of variance for continuous variables. For these analyses, the entire range of subjects (e.g., those with and without AUDs) was used to compare the results of Grant et al. (2004) and to determine if the earlier COGA results remained for this more broad population. For those items significantly differentiating across the three groups overall, chi-square or Tukey post hoc evaluations were used to evaluate how each of the three groups compared with the others. For the relevant tables, effect sizes are offered using the method described by Cohen (1992). Subsequently, simultaneous entry logistic regression analyses were used to evaluate the combination of variables from the prior analyses that best predicted independent and substance-induced MDEs, while noting the proportion of the variance explained as a pseudo R^2 statistic.

Results

Among the 2,548 subjects, 13.9% had been original probands from COGA families, 69.9% were their relatives, and 17.2% came from comparison families, with these groups representing COGA study participants interviewed in Phase II between January 1997 and January 2005. The mean (SD) age of the population was 31.6 (9.88) years old. They averaged 13.3 (1.99) years of education and consisted of 47.7% men. Regarding racial background, 71.5% were white, 18.9% were black, 6.9% were Hispanic, and 2.7% were of other backgrounds. At the time of interview, 61.0% were currently married, 6.2% were divorced, 0.4% were widowed, and 32.4% had never been married. The self-reported religious preferences were 43.6% Protestant, 33.3% Catholic, and 2.6% other; 20.5% listed no religion.

For the major analyses, these 2,548 subjects were divided into three groups based, first, on if they had ever experienced a DSM-IV independent MDE (n = 351 or 13.8%) and, from the remainder, if they had reported ever having a substance-induced mood disorder (238 or 9.3% of the total), along with 1,959 subjects (76.9%) who reported neither type of MDE. An additional 24 individuals were excluded because they did not fit clearly into these three categories, including 8 with independent manic depressive disease, 7 with independent dysthymia, and 9 with induced mania or dysthymia in the absence of independent or induced MDEs.

Table 1 compares the demographic characteristics across the three groups (independent, induced, and no MDE, shown as Groups 1-3, respectively). Subjects reporting only substance-induced MDEs (Group 2) differed from those with independent major depressions (Group 1) by having a larger proportion of probands, fewer subjects from comparison families, a lower proportion of women, fewer whites, and lower educational achievement. The major groups did not differ significantly on marital status or religion (e.g., proportion Protestant), although, compared with those with no MDE, members of both Groups 1 and 2 were a bit older. When the data in Table 1 were evaluated separately for alcoholics (N = 1,227) and nonalcoholics (N = 1,321), the demographic patterns and their relationships to the three MDE categories were generally similar for those with and without AUDs.

The higher proportion of probands and lower education for subjects with a history of substance-induced MDEs may indicate a more severe course of alcoholism for Group 2 subjects. This interpretation is supported by the data in Table 2, which compare groups on alcohol-related patterns. Here, as one might predict, compared with those in Group 1, subjects reporting histories of only substance-induced major depressions were more likely to have an AUD or an SUD. Group 2 subjects also reported a higher number of DSM-IV abuse or dependence items and higher maximum drinks in 24 hours. Regarding drugs ever used, the differences across Groups 1 and 2 were most notable for marijuana (30.2% vs 60.9%; χ^2 = 54.75), cocaine (14.0% vs 37.8%; χ^2 = 44.76), amphetamines (11.4% vs 25.6; χ^2 = 20.83), sedative/hypnotics (3.7% vs 14.7; χ^2 = 22.94), and opioids (4.3% vs 13.4%; χ^2 = 16.25), with the p value for

TABLE 1. Demographic characteristics of 2,548 COGA subjects divided by major depression

Variable	All subjects (N = 2,548)	Group 1 Independent MDE (n = 351)	Group 2 Induced MDE (n = 238)	Group 3 No mood dx (n = 1,959)	Overall F or χ^2	Independent vs induced Tukey or χ^2 (effect size)[a]	Independent vs no mood Tukey or χ^2 (effect size)[a]	Induced vs no mood Tukey or χ^2 (effect size)[a]
Proband, %	13.9	14.5	32.8	11.4	81.12‡	c (m)	–	c (s)
Comparison family, %	17.2	12.8	6.3	19.3	30.63‡	b (s)	b (s)	c (s)
Age, mean (SD)	31.6 (9.88)	33.7 (10.36)	33.3 (9.03)	31.0 (9.82)	15.44‡	–	c (s)	b (s)
Female gender, %	52.3	70.1	50.8	49.3	51.73‡	c (s)	c (s)	–
White race, %	71.5	82.1	70.2	69.8	22.23‡	c (s)	c (s)	–
Married, %	61.0	63.0	66.4	60.0	4.33	–	–	–
Education, mean (SD)	13.3 (1.99)	13.4 (1.95)	12.7 (1.95)	13.3 (1.99)	10.71‡	c (s)	–	c (s)
Protestant, %	43.6	41.3	45.4	43.8	1.09	–	–	–

Notes: COGA = Collaborative Study on the Genetics of Alcoholism; MDE = major depressive episode; dx = diagnosis. [a]Magnitude of effect as described by Cohen: Ω^2 for F (.01 small = s; .06 medium = m; .15 large = l); w for χ^2 (.10 small = s; .30 medium = m; .50 large = l).
‡$p < .001$.

all differences being <.001. Similarly, those with induced MDEs were more likely to have been smokers and to have fulfilled criteria for ASPD. Finally regarding Table 2, only subjects with induced major depressions, but not those with independent mood disorders, were significantly more likely than those with no MDE diagnosis to have a family history of AUDs. Once again, similar patterns for the way variables related to MDE groups were seen for alcoholic and nonalcoholic subjects, especially for maximum drinks and drug-related items, although, of course, the AUD diagnosis was not applicable to these evaluations.

Data related to histories of depressive disorders are presented in Table 3. For these analyses, information about Group 3 was generated from symptoms reported by subjects who had depressions lasting less than 2 weeks and those with longer depressions that did not meet MDE criteria, with those with no such episodes coded as zero. Regarding depressive symptoms during the most severe MDE, only those with independent depressions, but not those with induced MDEs, were more likely than those with no mood disorders (Group 3) to have a family history of independent depressions and were also less likely to report a notable weight change when depressed. Otherwise, the pattern of depressive symptoms during the most severe MDE was quite similar for Groups 1 and 2, including equal proportions with suicide attempts or psychiatric hospitalizations. Again, similar relationships of MDE diagnosis groups to the variables in Table 3 were seen for alcoholic and nonalcoholic subgroups.

The results from Tables 1 through 3 indicate that subjects with independent major depressions differed from those who experienced only substance-induced MDEs on a range of demographic and substance-related characteristics, as well as on the family history of independent MDEs. Table 4 explores how these differences performed when considered together in two separate logistic regression analyses predicting independent or induced MDEs among the 2,548 subjects. Background variables for which significant differences were observed for Groups 1 or 2, compared with the no-mood diagnosis Group 3, were entered into the relevant regression for all 2,548 participants, along with the family history items. There were exceptions related to the number

TABLE 2. Substance-related characteristics of 2,548 COGA subjects divided by major depression

Variable	All subjects (N = 2,548)	Group 1 Independent MDE (n = 351)	Group 2 Induced MDE (n = 238)	Group 3 No mood dx (n = 1,959)	Overall F or χ^2	Independent vs induced Tukey or χ^2 (effect size)[a]	Independent vs no mood Tukey or χ^2 (effect size)[a]	Induced vs no mood Tukey or χ^2 (effect size)[a]
Alcohol-use disorder, %	48.2	53.8	80.7	43.2	124.73‡	c (m)	c (s)	c (m)
Total 11 DSM-IV alcohol items, mean (SD)	2.7 (3.17)	3.3 (3.57)	5.8 (3.63)	2.2 (2.77)	164.98‡	c (m)	c (s)	c (m)
Max. drinks, mean (SD)	15.8 (13.25)	15.8 (13.56)	24.4 (15.58)	14.7 (12.49)	59.04‡	c (m)	–	c (s)
Any drug dx, %	35.6	37.0	71.8	30.9	155.33‡	c (m)	a (s)	c (m)
No. drug dx's, mean (SD)	0.6 (1.02)	0.6 (1.02)	1.5 (1.40)	0.5 (0.90)	118.51‡	c (m)	a (s)	c (m)
Smoke (≥10/day), %	41.4	51.6	62.6	37.0	74.64‡	b (s)	c (s)	c (s)
ASPD dx, %	10.2	13.1	24.4	8.0	66.08‡	c (s)	b (s)	c (s)
FH alcohol, %	43.0	45.3	50.4	41.7	7.44*	–	–	b (s)

Notes: COGA = Collaborative Study on the Genetics of Alcoholism; MDE = major depressive episode; dx = diagnosis; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; max. = maximum; ASPD = antisocial personality disorder; FH = family history. [a]Magnitude of effect as described by Cohen: Ω^2 for F (.01 small = s; .06 medium = m; .15 large = l); w for χ^2 (.10 small = s; .30 medium = m; .50 large = l).
*$p < .05$; ‡$p < .001$.

TABLE 3. Depressive symptoms of 2,548 COGA subjects divided by major depression

Variable	All subjects (N = 2,548) %	Group 1 Independent MDE (n = 351) %	Group 2 Induced MDE (n = 238) %	Group 3 No mood dx (n = 1,959) %	Overall F or χ^2	Independent vs induced Tukey or χ^2 (effect size)[a]	Independent vs no mood Tukey or χ^2 (effect size)[a]	Induced vs no mood Tukey or χ^2 (effect size)[a]
Suicide attempt	10.3	29.3	28.2	4.7	284.72‡	–	c (m)	c (m)
Psych. hospital	10.5	28.2	33.2	4.5	322.05‡	–	c (m)	c (m)
FH independent mood	19.4	27.1	22.3	17.7	17.99‡	–	c (s)	–
Specific depression symptoms								
Depression	41.0	98.6	96.6	23.9	1,021.71‡	–	c (l)	c (l)
Interest	40.9	98.0	97.5	23.8	1,026.65‡	–	c (l)	c (l)
Weight	30.3	72.6	81.9	16.4	776.81‡	b (s)	c (l)	c (l)
Insomnia	37.7	93.7	92.4	21.0	1,004.38‡	–	c (l)	c (l)
Agitation	23.5	61.4	65.5	11.6	670.04‡	–	c (l)	c (l)
Fatigue	34.1	86.9	84.9	18.5	917.92‡	–	c (l)	c (l)
Worthlessness	31.4	80.1	85.3	16.1	917.73‡	–	c (l)	c (l)
Concentration	33.9	88.9	87.3	17.6	1,006.16‡	–	c (l)	c (l)
Suicidal thoughts/attempt	20.5	58.0	60.3	8.9	694.88‡	–	c (l)	c (l)
No. mood symptoms, mean (SD)	2.9 (3.46)	7.4 (1.26)	7.5 (1.21)	1.6 (2.67)	1,323.47‡	–	c (l)	c (l)

Notes: COGA = Collaborative Study on the Genetics of Alcoholism; MDE = major depressive episode; dx = diagnosis; psych. = psychiatric; FH = family history. [a]Magnitude of effect as described by Cohen: Ω^2 for F (.01 small = s; .06 medium = m; .15 large = l); w for χ^2 (.10 small = s; .30 medium = m; .50 large = l).
‡$p < .001$.

of DSM alcohol items and maximum drinks (which overlapped with the AUD diagnosis) and the notation of one or more drug diagnoses (which overlapped with the number of diagnoses). The results for the prediction of independent MDEs explained 9% of the variance, with significant contributors that included an older age, female gender, white race, an ASPD diagnosis, and a family history of independent major depressive disorders. In contrast, the equation for the prediction of substance-induced MDEs explained 19% of the variance, with significant contributions from the proband status, being in a COGA (rather than comparison) family, having an AUD diagnosis, and having a greater number of illicit drug diagnoses of abuse or dependence.

Although the use of separate regressions most clearly presents the predictors of substance-induced versus independent MDEs, the data can also be evaluated using multinomial logistic regression. The same set of predictors was used for prediction of the two groups (i.e., all variables in Column 1 of Table 4), and the no MDE (Group 3) was used as a reference group. The resulting equation explained 20% of the variance, and, with few exceptions, these analyses revealed the same predictors of the two outcomes as described previously. In the multinomial approach, one additional predictor of independent MDEs emerged (smoking), whereas two additional predictors were noted for induced depressions (male gender and ASPD diagnoses).

Several additional analyses were also performed to explore more fully the results in Table 4. First, because the prior COGA article (Schuckit et al., 1997) focused only on subjects with AUDs (rather than the full COGA sample), to compare present and prior data, it was important to re-evaluate the current data set using the 1,227 subjects with lifetime histories of alcohol abuse or dependence. Among these, 189 individuals (15.4% of the 1,227 alcoholics) had an independent mood disorder, and 192 individuals (15.6%) had only a substance-induced MDE. When the logistic regressions reported in Table 4 were repeated predicting independent and induced depressions among alcoholics, the results changed little from those reported in the table. For independent depressions, the equation explained 13% of the variance, with significant predictors including older age, female gender, white race, an ASPD diagnosis, and a family history of independent mood disorders. The smoking status also contributed to the prediction of independent depressions (OR = 1.53, $p < .05$). For substance-induced MDEs, 13% of the variance was also explained, with significant predictors including proband status and the number of drug diagnoses. In that equation among alcoholics, ASPD also contributed (OR = 1.5, $p < .05$), but, of course,

TABLE 4. Separate logistic regressions predicting independent and induced major depressive episodes (MDEs), odds ratios

Variables	Independent MDE	Induced MDE
Proband	NA	2.40‡
Comparison family	0.81	0.47†
Age	1.02‡	0.99
Gender	2.85‡	NA
White	1.84‡	NA
Education	NA	0.94
Alcohol-use disorder	1.21	2.36‡
No. of drug dx's	0.95	1.50‡
Smoke	1.29	1.06
ASPD dx	1.97‡	1.40
FH alcohol	NA	1.15
FH independent MDE	1.71‡	NA
Pseudo R^2	.09	.19

Notes: ASPD = antisocial personality disorder; dx = diagnosis; FH = family history.
†$p < .01$; ‡$p < .001$.

the AUD diagnosis was not used as a predictor. When the regression was repeated for the 1,321 nonalcoholics, 7% of the variance for predicting independent MDEs was explained, with predictors including female gender, white race, and a family history of independent MDEs, with ASPD narrowly missing significance ($p = .06$) but age and smoking dropping out. For induced MDEs in nonalcoholics, only 46 individuals had consumed enough alcohol at the onset of a depressive episode to have been considered to have had an induced MDE. For them, the regressions predicting induced MDEs explained 10% of the variance, with OR values very similar to those reported in Table 4, although, reflecting the relatively small sample, only the number of drug diagnoses was a significant contributor.

Another set of additional analyses evaluated if some of the differences between earlier COGA results (Schuckit et al., 1997) and the general population protocol reported by Grant et al. (2004) might reflect the high density of AUDs in COGA families. Therefore, evaluations were performed separately for the 438 participants who came from comparison families and for the 2,110 individuals who came from COGA pedigrees. Among comparison families, the logistic regressions predicting independent MDEs explained 13% of the variance, with significant contributions from female gender and a trend for contribution by a diagnosis of ASPD ($p = .07$). The predictors of substance-induced MDEs combined to explain 25% of the variance, with the major contributor being the number of drug diagnoses. The performance of the regressions in the COGA families revealed 9% and 17% of the variance explained for independent and induced MDEs, respectively, with predictors similar to those in Table 4 but with, in addition, AUDs predicting independent MDEs.

Discussion

Diagnosis in psychiatry is challenging, at least in part because the same clinical picture (e.g., intense sadness) can be seen in several different disorders. The need to develop a thoughtful differential diagnosis for psychiatric syndromes is especially relevant to individuals consuming high doses of alcohol and most substances of abuse, because these agents affect brain functioning and often lead to conditions that temporarily mimic independent psychiatric disorders (Schuckit, 2006).

Not all studies agree on the prevalence and clinical importance of substance-induced disorders, especially as they relate to substance-induced depressions. For example, a survey of more than 40,000 subjects from the general U.S. population used about 1,800 research assistants to administer a fully structured interview and reported that less than 1% of the general population had a substance-induced MDE in the prior year (Grant et al., 2004). However, if all the substance-induced conditions had been observed among the 4% of the studied population with an AUD or an SUD, almost 30% of the total depressions observed in those subjects may have been substance induced. Several other investigations have noted even higher lifetime rates of substance-induced depressions among alcoholics, with numbers often ranging between 40% and 60% of the depressions reported (Gilder et al., 2004; Hesselbrock et al., 2003; Schuckit et al., 1997). The largest of these studies was based on almost 3,000 alcohol-dependent subjects reporting that more than 60% of the lifetime MDEs had been substance induced, with the distinction between induced and independent MDEs supported by several external validators. The differences in results between the 2004 epidemiological survey (Grant et al., 2004) and the earlier COGA investigation (Schuckit et al., 1997) could have reflected differences in the rates of AUDs in the populations studied (i.e., the general population, 96% of whom did not have an AUD or SUD, vs alcoholic subjects in the 1997 COGA study), the time frame (1 year vs lifetime), the type of interviews (e.g., a fully structured vs a semistructured approach using a smaller number of closely supervised interviewers who were encouraged to probe for clarification of answers), and the fact that the COGA study used data generated almost a decade before the 1994 national sample investigation.

The present analyses corroborate the earlier COGA results using data from an updated Phase II version of the semistructured interview, expanding the earlier study to include nonalcoholics in a more contemporary sample and evaluating subjects from comparison as well as COGA families. Approximately 50% of the MDEs in alcoholics were substance induced, and the correlates of independent and substance-induced depressions were almost identical to those reported a decade earlier. Most notable is the finding that, as one might predict for independent depressive episodes, individuals with this label were still more likely to be female, to be white, and to have a family history of independent MDEs. Subjects with substance-induced depressions (but not independent MDEs) were distinguished primarily by items that were likely to reflect the severity of their AUDs and drug-use disorders. These similarities to the earlier COGA results persisted despite the use of a new and updated interview; were observed among subjects, the large majority of whom had not participated in the earlier COGA investigation; and remained robust among both alcoholics and nonalcoholics and in COGA, as well as comparison families.

The higher proportion of women among individuals with independent (but not substance-induced) MDEs is consistent with the pattern of MDEs in the general population (Kessler et al., 2003). Regarding the racial breakdown, at least one investigation using data from a national epidemiological study reported a risk for MDEs that was significantly higher among white groups, compared with black and Hispanic populations (Riolo et al., 2005). A similar

result regarding racial distributions for independent versus induced disorders had also been reported in the earlier COGA analyses (Schuckit et al., 1997).

ASPD was an additional correlate of MDEs in the current study. Conclusions regarding this label from Table 2 appear to be most robust for induced depressions, in which 24.4% of those with induced MDEs—compared with 13.1% of those with independent MDEs—carried an ASPD diagnosis. This finding could reflect more prominent pharmacological effects of alcohol resulting from the more intense alcohol-related problems among ASPD subjects (Harford and Muthén, 2000). However, ASPD also related to independent MDEs and added significantly to the regression in Table 4 predicting independent, but not induced, depressions. The latter may have reflected the inability of ASPD to contribute anything to the equation for induced disorders once proband status (i.e., more severe alcoholism) and alcohol and drug diagnoses were considered. However, other studies have reported an elevated rate of what might be independent depressions in antisocial individuals (Darke et al., 2003; Fu et al., 2002).

This study also offers potentially useful information about the prevalence of substance-induced MDEs across several subgroups. First, only 9.3% of the subjects in Table 1 ever had an induced mood disorder, and 13.8% had an independent MDE (the latter is a rate similar to what is expected in the general population); however, those data relate to a mixed group of alcoholics and subjects with no substance-related disorder. When alcoholics were evaluated separately, 15.4% had a lifetime history of an independent MDE, and 15.6% had a substance-induced depressive episode. Thus, alcoholics did not appear to have a marked increased risk for independent MDEs, and slightly more than half of the depressions observed at some point in their lives were substance-induced conditions. This proportion of induced disorders may be an underestimate of the actual prevalence among individuals with AUDs, because the structure of the SSAGA precluded a full determination of the rate of induced depressions among individuals who reported an independent depressive condition as their most severe depression. Non-AUD subjects could have had substance-induced depressions during periods of heavier drinking. The conclusion that approximately half of the depressions reported among alcoholics in their lifetime were substance induced was noted in both COGA alcoholic and comparison families not originally chosen because of an alcoholic relative. However, it is unfortunate that the structure of the SSAGA did not fully address the question of whether having a history of independent depressions increased the probability of developing an induced depression in the context of heavy drinking. This is especially important because of possible genetic links between a predisposition toward AUDs and mood disorders in general, and the possibility that some alcoholics and their relatives may be more prone to alcohol-induced MDEs than others (Nurnberger et al., 2004).

Another important observation is that the patterns of symptoms during the most severe MDEs were very similar for independent and induced mood disorders. Thus, despite additional data documenting the probability that induced depressions are likely to clear soon after abstinence (Brown et al., 1995; Davidson, 1995), researchers and clinicians may not be able to differentiate between these two clinical conditions with different prognoses based on symptoms alone, and they need to consider using the timeline-based approach based on a DSM-IV algorithm described in this study. Although it is possible that genetic and brain-imaging findings in the future might help establish induced versus independent conditions, at present, the timeline approach is the only tool available to distinguish between these disorders.

In viewing these results, as well as in comparing the current data with other studies, it is important to keep the methodologies in mind. First, the majority of subjects came from COGA families, originally chosen because of an alcohol-dependent individual who had entered and who had multiple additional alcoholic relatives. However, the same general findings appeared to operate among alcoholics and nonalcoholics, as well as among subjects from COGA versus comparison families. Second, at least in part as a reflection of the highly complex nature of the COGA data set, as well as our emphasis on establishing diagnoses from directly interviewed individuals only, the family history data reported here relate only to parents of the subject. Third, this study focused on lifetime (as opposed to prior 12-month) diagnoses, with the result that data from the prior years might have generated different results. In addition, although the SSAGA is an extensive instrument, all data were retrospective and based on self-reports. Finally, neither COGA nor comparison families are likely to be representative of the overall U.S. population, and, thus, the generalizability of these findings needs to be carefully established.

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References

Altamura, A.C., Mauri, M.C., Girardi, T., and Panetta, G. Alcoholism and depression: A placebo controlled study with viloxazine. Int. J. Clin. Pharmacol. Res. **10:** 293-298, 1990.

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R), Washington, DC, 1987.

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Text Revision (DSM-IV-TR), Washington, DC, 2000.

Brown, S.A., Inaba, R.K., Gillin, J.C., Schuckit, M.A., Stewart, M.A., and Irwin, M.R. Alcoholism and affective disorder: Clinical course of depressive symptoms. Amer. J. Psychiat. **152:** 45-52, 1995.

Bucholz, K.K., Cadoret, R., Cloninger, C.R., Dinwiddie, S.H., Hesselbrock, V.M., Nurnberger, J.I., Jr., Reich, T., Schmidt, I., and Schuckit, M.A. A new, semi-structured psychiatric interview for use in genetic linkage studies: A report on the reliability of the SSAGA. J. Stud. Alcohol **55:** 149-158, 1994.

Cohen, J. A power primer. Psychol. Bull. **112:**155-159, 1992.

Darke, S., Ross, J., and Lynskey, M. The relationship of conduct disorder to attempted suicide and drug use history among methadone maintenance patients. Drug Alcohol Rev. **22:** 21-25, 2003.

Davidson, K.M. Diagnosis of depression in alcohol dependence: Changes in prevalence with drinking status. Brit. J. Psychiat. **166:** 199-204, 1995.

Feighner, J.P., Robins, E., Guze, S.B., Woodruff, R.A., Jr., Winokur, G., and Munoz, R. Diagnostic criteria for use in psychiatric research. Arch. Gen. Psychiat. **26:** 57-63, 1972.

Fu, Q., Heath, A.C., Bucholz, K.K., Nelson, E., Goldberg, J., Lyons, M.J., True, W.R., Jacob, T., Tsuang, M.T., and Eisen, S.A. Shared genetic risk of major depression, alcohol dependence, and marijuana dependence: Contribution of antisocial personality disorder in men. Arch. Gen. Psychiat. **59:** 1125-1132, 2002.

Gilder, D.A., Wall, T.L., and Ehlers, C.L. Comorbidity of select anxiety and affective disorders with alcohol dependence in Southwest California Indians. Alcsm Clin. Exp. Res. **28:** 1805-1813, 2004.

Grant, B.F., Stinson, F.S., Dawson, D.A., Chou, S.P., Dufour, M.C., Compton, W., Pickering, R.P., and Kaplan, K. Prevalence and co-occurrence of substance use disorders and independent mood and anxiety disorders: Results from the National Epidemiologic Survey on Alcohol and Related Conditions. Arch. Gen. Psychiat. **61:** 807-816, 2004.

Harford, T.C. and Muthén, B.O. Adolescent and young adult antisocial behavior and adult alcohol use disorders: A fourteen-year prospective follow-up in a national survey. J. Stud. Alcohol **61:** 524-528, 2000.

Hasin, D.S., Goodwin, R.D., Stinson, F.S., and Grant, B.F. Epidemiology of major depressive disorder: Results from the National Epidemiologic Survey on Alcoholism and Related Conditions. Arch. Gen. Psychiat. **62:** 1097-1106, 2005.

Hasin, D.S. and Grant, B.F. Major depression in 6050 former drinkers: Association with past alcohol dependence. Arch. Gen. Psychiat. **59:** 794-800, 2002.

Hasin, D., Liu, X., Nunes, E., McCloud, S., Samet, S., and Endicott, J. Effects of major depression on remission and relapse of substance dependence. Arch. Gen. Psychiat. **59:** 375-380, 2002.

Hesselbrock, M., Easton, C., Bucholz, K.K., Schuckit, M., and Hesselbrock, V. A validity study of the SSAGA—A comparison with the SCAN. Addiction **94:** 1361-1370, 1999.

Hesselbrock, M.N., Hesselbrock, V.M., Segal, B., Schuckit, M.A., and Bucholz, K. Ethnicity and psychiatric comorbidity among alcohol-dependent persons who receive inpatient treatment: African Americans, Alaska Natives, Caucasians, and Hispanics. Alcsm Clin. Exp. Res. **27:** 1368-1373, 2003.

Isbell, H., Fraser, H.F., Wikler, A., Belleville, R.E., and Eisenman, A.J. An experimental study of the etiology of "rum fits" and delirium tremens. Q. J. Stud. Alcohol **16:** 1-33, 1955.

Kessler, R.C., Berglund, P., Demler, O., Jin, R., Koretz, D., Merikangas, K.R., Rush, A.J., Walters, E.E., and Wang, P.S. National Comorbidity Survey Replication: The epidemiology of major depressive disorder. Results from the National Comorbidity Survey Replication (NCS-R). JAMA **289:** 3095-3105, 2003.

Kessler, R.C., Chiu, W.T., Demler, O., Merikangas, K.R., and Walters, E.E. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. Arch. Gen. Psychiat. **62:** 617-627, 2005.

Kessler, R.C., Crum, R.M., Warner, L.A., Nelson, C.B., Schulenberg, J., and Anthony J.C. Lifetime co-occurrence of DSM-III-R alcohol abuse and dependence with other psychiatric disorders in the National Comorbidity Survey. Arch. Gen. Psychiat. **54:** 313-321, 1997.

Kessler, R.C., McGonagle, K.A., Zhao, S., Nelson, C.B., Hughes, M., Eshleman, S., Wittchen, H.-U., and Kendler, K.S. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States: Results from the National Comorbidity Survey. Arch. Gen. Psychiat. **51:** 8-19, 1994.

Kiefer, F. and Barocka, A. Secondary depression in weaned alcoholics: Implications of Lesch's typology of chronic alcoholism. Alcohol Alcsm **34:** 916-917, 1999.

Nurnberger, J.I., Jr., Wiegand, R., Bucholz, K., O'Connor, S., Meyer, E.T., Reich, T., Rice, J., Schuckit, M., King, L., Petti, T., Bierut, L., Hinrichs, A.L., Kuperman, S., Hesselbrock, V., and Porjesz, B. A family study of alcohol Dependence: Coaggregation of multiple disorders in relatives of alcohol-dependent probands. Arch. Gen. Psychiat. **61:** 1246-1256, 2004.

Riolo, S.A., Nguyen, T.A., Greden, J.F., and King, C.A. Prevalence of depression by race/ethnicity: Findings from the National Health and Nutrition Examination Survey III. Amer. J. Publ. Hlth **95:** 998-1000, 2005.

Schuckit, M.A. Comorbidity between substance use disorders and psychiatric conditions. Addiction **101** (Suppl. No. 1): 76-88, 2006.

Schuckit, M.A., Irwin, M., and Smith, T.L. One-year incidence rate of major depression and other psychiatric disorders in 239 alcoholic men. Addiction **89:** 441-445, 1994.

Schuckit, M.A., Tipp, J.E., Bergman, M., Reich, W., Hesselbrock, V.M., and Smith, T.L. Comparison of induced and independent major depressive disorders in 2,945 alcoholics. Amer. J. Psychiat. **154:** 948-957, 1997.

Slutske, W.S., Heath, A.C., Dinwiddie, S.H., Madden, P.A.F., Bucholz, K.K., Dunne, M.P., Statham, D.J., and Martin, N.G. Common genetic risk factors for conduct disorder and alcohol dependence. J. Abnorm. Psychol. **107:** 363-374, 1998.

Tamerin, J.S., Weiner, S., and Mendelson, J.H. Alcoholics' expectancies and recall of experiences during intoxication. Amer. J. Psychiat. **126:** 1697-1704, 1970.

Willenbring, M.L. Measurement of depression in alcoholics. J. Stud. Alcohol **47:** 367-372, 1986.

Winokur, G., Coryell, W., Endicott, J., Keller, M., Akiskal, H., and Solomon, D. Familial alcoholism in manic-depressive (bipolar) disease. Amer. J. Med. Genet. (Part B: Neuropsychiat. Genet.) **67:** 197-201, 1996.