ORIGINAL ARTICLE

Long-term Stability of Alcohol and Other Substance Dependence Diagnoses and Habitual Smoking

An Evaluation After 5 Years

Robert Culverhouse, PhD; Kathleen K. Bucholz, PhD; Raymond R. Crowe, MD; Victor Hesselbrock, PhD; John I. Nurnberger, Jr, MD, PhD; Bernice Porjesz, PhD; Marc A. Schuckit, MD; Theodore Reich, MD†; Laura Jean Bierut, MD

Context: A major criterion to validate diagnoses is stability over time.

Objective: To examine the stability of several classification systems for lifetime diagnosis of alcohol dependence, to identify characteristics predicting stability of alcoholism, and to study stability of lifetime assessments of habitual smoking (1 pack per day for at least 6 months) and other drug dependence.

Design: Participants in the Collaborative Study on the Genetics of Alcoholism were interviewed using the Semi-Structured Assessment for the Genetics of Alcoholism and reevaluated 5 years later. Initial and follow-up interviews were available for 1728 individuals (641 index cases, 800 siblings, 287 controls) with lifetime diagnoses of alcohol dependence, other substance dependence (marijuana, cocaine, other stimulants, sedatives, opioids), or habitual smoking at first interview. The likelihood that an individual with a lifetime history of substance dependence or habitual smoking at the first interview retained this classification after 5 years was examined to assess stability of diagnosis.

Results: Stability of a lifetime diagnosis of alcohol dependence varied among the subject groups of index cases, siblings, and community-based controls. Alcohol dependence as defined by *DSM-III-R* criteria was highly stable in the index cases (90.5% women, 94.7% men) but much less stable in the community-based controls (27.5% women, 64.7% men). The most important characteristic associated with stability of diagnosis of alcohol dependence was severity, defined by the number of alcohol-related symptoms. Other *DSM-III-R* substance dependence disorders varied in the stability of diagnosis over a 5-year period. Lifetime history of habitual smoking was highly stable in all subject groups (96.0% overall).

Conclusions: Stability of lifetime assessment of alcohol dependence varies depending on severity of illness. Severe cases of alcohol dependence are more likely to be stable, whereas general population cases of alcohol dependence are less likely to have stable diagnoses. The stability of diagnosis for other substance dependence varies from substance to substance.

Arch Gen Psychiatry. 2005;62:753-760

THE JUDICIOUS DEVELOPMENT of diagnostic criteria is essential in the study of complex clinical illnesses. Alcohol and other substance dependence disorders, along with most psychiatric disorders, fall into the category of illnesses diagnosed by clinical presentations alone. With no specified laboratory values to serve as a gold standard, the validity of these disorders is particularly difficult to evaluate. Stability of classification systems over time is a key factor in establishing the validity of diagnostic criteria.[1,2]

Stability of diagnosis, ie, same classification over 2 or more time points, is an indicator of a true diagnosis. Subjects that are mistakenly diagnosed as affected are less likely than correctly diagnosed subjects to retain a lifetime diagnosis years later. Although some measurements of epidemiological interest (such as estimates of population prevalence) may be robust to a moderate amount of misclassification, even a small amount of diagnostic misclassification can greatly reduce the ability to detect differences between affected and unaffected subjects in the study of diseases. For these reasons, the identification of factors contributing to the stability of diagnosis, including psychiatric illnesses, can be a powerful tool for the design of future studies. Alcoholism and other substance dependence have been found to be among the most reliably as-

Author Affiliations are listed at the end of this article.
†Deceased.

sessed psychiatric disorders.[3,4] Numerous standardized psychiatric instruments have shown high reliability in short-term (1 week) reassessments of alcoholism and other substance dependence diagnoses in populations such as the genetic study subjects,[5] subjects in substance abuse treatment settings,[6,7] in the general US population,[8] in a sample of Puerto Rican medical patients,[9] and in international populations.[10] Long-term reliability for the assessment of alcoholism symptoms is also high.[11-13]

To extend these findings, this study undertook the examination of the 5-year stability of a lifetime diagnosis of alcoholism and other substance dependence using data from the Collaborative Study on the Genetics of Alcoholism (COGA). The broad-ranging scope of the signs and symptoms surveyed by the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA)[14] allowed comparative analyses not only of different diagnostic classification systems for alcohol dependence, but also of habitual smoking and dependence on other substances including marijuana, cocaine, other stimulants, sedatives, and opioids. Stability was defined as the percentage of those individuals who received a lifetime diagnosis of a disorder at the initial assessment and who also obtained a lifetime diagnosis of the same disorder at a 5-year reassessment. All instances where the classification was not retained represent clear errors in diagnosis, either at the first or second assessment.

Three study questions were examined:

1. Does the stability of alcohol dependence (defined as the percentage of individuals with a lifetime diagnosis at initial assessment who retain the diagnosis at reassessment) differ depending on the classification system (ie, *DSM-III-R*, *DSM-IV*, *International Classification of Diseases, 10th Revision* [*ICD-10*] criteria) used?
2. What demographic and clinical characteristics predict which individuals will have stable diagnoses of alcohol dependence?
3. Does the stability of alcohol dependence differ from the stability of dependence on other substances?

METHODS

The COGA is a large-scale family and genetic study with 6 data collection sites: Indiana University, Indianapolis; State University of New York Health Sciences Center, Brooklyn; University of California, San Diego; University of Connecticut, Farmington; University of Iowa, Iowa City; and Washington University in St Louis, St Louis, Mo. The protocol was approved by institutional review boards at all sites and written informed consent was obtained from all subjects. Data available as of June 2003 were used in the current analysis.

SUBJECTS

Index cases, or probands, were identified in public and private chemical dependency treatment settings, both inpatient and outpatient. To be included in the study, probands (English speaking and 18 years of age or older) were required to meet lifetime criteria for both *DSM-III-R* alcohol dependence[15] and the Feighner et al[2] criteria for definite alcoholism. Meeting these joint criteria was designated as "COGA alcoholism." Because COGA is a family study, probands were also required to have at least 2 first-degree relatives who were available for study and were living in one of the COGA catchment areas. Probands were excluded if they had a life-threatening illness, severe cognitive impairment, acute psychosis, habitual intravenous drug use (>30 times lifetime or any intravenous drug use in the last 6 months), or human immunodeficiency virus infection. All available first-degree relatives of probands were invited to participate in the study. The COGA probands and their participating first-degree biological relatives constitute the COGA families.

Control families, recruited to estimate the general population rate of alcoholism and related disorders in families, were ascertained by a variety of strategies, including sampling from members of health maintenance organizations, from dental clinics, and from driver's license bureaus. Alcohol dependence, drug dependence, or other psychiatric disorders were not exclusionary criteria for control families. Control families contained 5 or more members: 2 parents and 3 or more offspring aged 14 or older.

ASSESSMENT

All subjects completed the SSAGA,[14] a highly reliable and valid[16] semistructured lay interview designed to assess lifetime diagnoses of alcohol abuse and dependence, dependence on other substances (including marijuana, cocaine, other stimulants, sedatives, and opioids), smoking, and other major psychiatric disorders. Interview data were reviewed by an editor, and after data entry, they were further screened for consistency.

Lifetime alcoholism diagnoses were made according to Feighner definite, *DSM-III-R*, COGA (Feighner definite plus *DSM-III-R*), *DSM-IV*,[17] and *ICD-10*[18] criteria. Though the SSAGA was developed prior to the publication of the *DSM-IV* criteria, all criteria symptoms for the *DSM-IV* diagnosis were queried, as well as times of onset and remission of symptoms. Clustering of symptoms for a *DSM-IV* diagnosis was determined by 2 means: clustering in a 1-month period was queried directly, while clustering within a 1-year period was imputed through analyses of onsets and remissions of symptoms. Other lifetime drug dependence diagnoses (marijuana, cocaine, other stimulants, sedatives, and opioids) were made according to *DSM-III-R* criteria. All classifications were made by computer programs that scored the interview data on the decision criteria for the diagnostic systems named above. Nicotine dependence was not evaluated in the initial assessment, so habitual smoking, defined as smoking at least 1 pack (20 cigarettes) daily for 6 months or more, was used as the categorization for smoking.

As part of the follow-up study, adult subjects were blindly reinterviewed after 5 years. The follow-up study targeted all probands, members of families severely affected with alcoholism (defined as having at least 3 members of the nuclear family diagnosed with alcoholism), members of families with youth aged 7 to 25 years, and all members of control families. Of eligible subjects, the

Table 1. Five-Year Stability of Lifetime Diagnoses of Alcohol Dependence

Subject Group	Sex	*DSM-III-R* Initially Diagnosed, No.	*DSM-III-R* Same Diagnosis After 5 y, No. (%)	Feighner Definite Initially Diagnosed, No.	Feighner Definite Same Diagnosis After 5 y, No. (%)	COGA* Initially Diagnosed, No.	COGA* Same Diagnosis After 5 y, No. (%)	*DSM-IV* Initially Diagnosed, No.	*DSM-IV* Same Diagnosis After 5 y, No. (%)	*ICD-10* Initially Diagnosed, No.	*ICD-10* Same Diagnosis After 5 y, No. (%)
Probands	Female	168	152 (90.5)	168	153 (91.1)	168	150 (89.3)	167	131 (78.4)	156	116 (74.4)
	Male	473	448 (94.7)	473	449 (94.9)	473	441 (93.2)	458	389 (84.9)	439	366 (83.4)
Siblings	Female	261	195 (74.7)	264	195 (73.9)	226	157 (69.5)	192	111 (57.8)	125	77 (61.6)
	Male	296	231 (78.0)	295	236 (80.0)	265	202 (76.2)	220	133 (60.4)	159	104 (65.4)
Controls	Female	40	11 (27.5)	36	14 (38.9)	22	7 (31.8)	25	5 (20.0)	7	3 (42.9)
	Male	102	66 (64.7)	90	62 (68.9)	65	45 (69.2)	57	18 (31.6)	26	14 (53.8)
Overall		1338	1102 (82.4)	1326	1109 (83.6)	1219	1002 (82.2)	1119	787 (70.3)	912	680 (74.6)

Abbreviations: COGA, Collaborative Study on the Genetics of Alcoholism; *ICD-10*, *International Classification of Diseases, 10th Revision*.
*The COGA diagnosis for alcohol dependence requires an individual to satisfy both *DSM-III-R* alcohol dependence and Feighner definite alcoholism criteria.

follow-up rate was 60% in probands, 65% in family members, and 78% in controls.

To assess stability of diagnosis, 3 adult groups were examined: probands, their siblings, and control subjects. Initial and follow-up SSAGA interviews were completed for 2757 adults: 641 COGA probands, 1232 of their adult siblings, and 884 adult control subjects. Of these, 1728 individuals (641 COGA probands, 800 siblings, 287 controls) had at least 1 lifetime diagnosis of alcohol or other substance (marijuana, cocaine, other stimulant, sedative, opioid) dependence, or habitual smoking on initial assessment. To examine the stability of selected diagnoses, individuals who had a lifetime history of the disorder of interest at the initial assessment were included in analyses. Since disorders were "lifetime," subjects affected at the initial assessment should have been affected at the follow-up assessment if the diagnoses were stable over time. A change from affected at initial assessment to unaffected at reassessment represents an error in diagnosis: either a false-positive diagnosis at initial interview or a false-negative diagnosis at follow-up.

To gain a better understanding of the factors that contribute to the stability of classification over time, alcohol dependence was examined more thoroughly. To this end, multiple features related to the stability of a lifetime history diagnosis of alcohol dependence were studied. First, the different systems for the diagnosis of alcohol dependence were analyzed (*DSM-III-R*, *DSM-IV*, Feighner definite, COGA alcoholism [*DSM-III-R* plus Feighner definite], and *ICD-10* criteria). To better understand the variables that contribute to the stability of diagnosis for alcoholism, univariate and multivariate logistic regression models were examined. Because alcohol dependence was the key ascertainment criterion for the COGA sample, the data had the most power to answer questions about this phenotype. Initial variables included in the analyses were birth cohort, sex, race, recruitment center, history of treatment for alcoholism, a severity index, comorbid habitual smoking and other substance dependence, and other comorbid diagnoses (major depressive disorder, conduct disorder, and antisocial personality disorder). Only those variables that were significant in univariate analyses were included in the multivariate analysis.

Finally, other substance dependence diagnoses (marijuana, cocaine, other stimulants, sedatives, and opioids) and habitual smoking were examined for stability. To be a stable case, a diagnosis of *DSM-III-R* criteria for the specific substance dependence had to be met at both the initial and follow-up assessments.

All statistical analyses were performed using SAS[19] version 6.11 on a Unix platform. Dependence rates were summarized using proportions. Univariate and multivariate analyses were performed using logistic regression.

RESULTS

STABILITY FOR DIFFERENT DEFINITIONS OF ALCOHOL DEPENDENCE

Of the individuals assessed twice, 1219 (641 probands, 491 siblings, 87 controls) met criteria for a lifetime diagnosis of COGA alcoholism at the initial assessment, and 82% of these retained the lifetime diagnosis of COGA alcoholism at the 5-year reassessment. The overall stabilities of the other definitions of alcoholism were 82% *DSM-III-R* alcohol dependence, 84% Feighner definite alcoholism, 70% *DSM-IV* alcohol dependence, and 75% *ICD-10* alcohol dependence. Overall, the diagnosis of alcohol dependence is stable across multiple classification criteria, with the broader criteria being slightly more stable.

The overall stability in the COGA sample obscures important characteristics of stability. **Table 1** lists the 5-year stability of lifetime diagnoses of alcoholism under each of the 5 definitions in relation to subject type (ie, COGA proband, sibling, or control) and sex. Some key trends were noted in these data. First, stability varied greatly among the subject groups. Diagnoses in probands were more stable than in their siblings, and stability of diagnoses in controls was more modest than in the other groups. Second, diagnoses were more stable in men than in women. These trends were present under each of the 5 classification systems and are consistent with the hypothesis that more severe illness results in more stable lifetime diagnoses.

Table 2. Likelihood of Receiving Lifetime Alcohol Dependence Diagnosis in Any Diagnostic System 5 Years After an Initial Lifetime Diagnosis of Alcohol Dependence

		Initial *DSM-III-R* Diagnosis		Initial Feighner Definite Diagnosis		Initial COGA* Diagnosis		Initial *DSM-IV* Diagnosis		Initial *ICD-10* Diagnosis	
Subject Group	Sex	Initially Diagnosed Under *DSM-III-R*, No.	Diagnosed Under Any System After 5 y, No. (%)	Initially Diagnosed Under Feighner Definite, No.	Diagnosed Under Any System After 5 y, No. (%)	Initially Diagnosed Under COGA, No.	Diagnosed Under Any System After 5 y, No. (%)	Initially Diagnosed Under *DSM-IV*, No.	Diagnosed Under Any System After 5 y, No. (%)	Initially Diagnosed Under *ICD-10*, No.	Diagnosed Under Any System After 5 y, No. (%)
Probands†	Female	168	158 (94.0)	168	158 (94.0)	168	158 (94.0)	167	157 (94.0)	156	149 (95.5)
	Male	473	459 (97.0)	473	459 (97.0)	473	459 (97.0)	458	445 (97.2)	439	428 (97.5)
Siblings	Female	261	212 (81.2)	264	216 (81.8)	226	192 (85.0)	192	170 (88.5)	125	116 (92.8)
	Male	296	253 (85.5)	295	254 (86.1)	265	237 (89.4)	220	201 (91.4)	159	148 (93.1)
Controls	Female	40	19 (47.5)	36	17 (47.2)	22	13 (59.1)	25	13 (52.0)	7	5 (71.4)
	Male	102	74 (72.5)	90	69 (76.7)	65	55 (84.6)	57	47 (82.5)	26	23 (88.5)

Abbreviations: COGA, Collaborative Study on the Genetics of Alcoholism; *ICD-10*, *International Classification of Diseases, 10th Revision*.
*The COGA diagnosis for alcohol dependence requires an individual to satisfy both *DSM-III-R* alcohol dependence and Feighner Definite alcoholism.
†Because all probands had a COGA diagnosis of alcohol dependence (combined diagnosis of *DSM-III-R* alcohol dependence and Feighner definite alcoholism), the first 3 columns for the probands are identical.

The information in Table 1 also suggests that more stringent criteria for the diagnosis of alcohol dependence (eg, *ICD-10*) generally resulted in diagnoses that were less stable at the 5-year reassessment. At first glance, this may seem at odds with the hypothesis that more severe alcohol dependence is more stable. However, while the narrowest criteria set (*ICD-10*) did not result in the most stable diagnosis, satisfying the *ICD-10* criteria at the initial assessment did increase the likelihood that an individual would be diagnosed as alcohol-dependent (under at least 1 of the definitions) after 5 years. **Table 2** displays the percentage of individuals meeting particular (lifetime) diagnostic criteria at baseline who meet any lifetime alcohol dependence definition at the 5-year follow-up. The trend of more severe initial syndrome leading to greater likelihood of retaining at least 1 lifetime alcohol dependence diagnosis at follow-up is particularly striking in the sample of siblings, which displays a greater range in severity (defined as number of symptoms endorsed) than the proband sample. For example, there were 125 female siblings initially diagnosed with *ICD-10* alcohol dependence. Only 77 (62%) of them retained the *ICD-10* lifetime diagnosis on the second interview, while 116 (93%) had a lifetime alcohol dependence diagnosis under at least 1 of the classification systems on their second interview. In addition, the stability of female controls, which was particularly low when defined as meeting the same diagnostic criteria (Table 1), increases substantially if stability is defined broadly as meeting any definition of alcohol dependence (Table 2).

Using "treatment" as a surrogate for severity of illness, stability of diagnosis in individuals who reported any treatment for alcoholism (including attending Alcoholics Anonymous meetings or other self-help treatment) was compared with the stability in those who did not report any treatment (**Table 3**). Once the subjects are stratified based on treatment, stability of diagnosis in siblings and controls is similar to that observed in probands, all of whom have been treated.

PREDICTORS OF STABILITY: ALCOHOL DEPENDENCE

To better understand which variables are useful in predicting stability of diagnosis, logistic regression analyses were performed with rediagnosis of COGA alcoholism as the outcome variable on the data set consisting of probands (N=641) and their siblings who met the definition of COGA alcohol dependence at the initial interview (N=491). Control subjects were not included since so few were diagnosed with COGA alcoholism at the initial interview (N=87).

First, univariate analyses were performed to examine variables that might influence stability: sex, birth cohort (born before 1950, born between 1950 and 1960, born after 1960), race, treatment for alcoholism, dependence on other substances (marijuana, cocaine, other stimulants, sedatives, opioids), habitual smoking, comorbid psychiatric conditions (major depressive disorder, conduct disorder, antisocial personality disorder), and severity of dependence (defined by the number of *DSM-III-R* criteria A symptoms endorsed: low, 3-4 criteria; moderate, 5-6 criteria; high, 7-8 criteria; maximum, 9 criteria). The percentages of the sample falling into each severity class were 17%, 25%, 32%, and 26%, respectively. Several significant predictors were found: sex, recruitment center, treatment for alcoholism, lifetime major depression, dependence on any other substance, and severity of illness (defined by symptom count). Birth cohort, race, conduct disorder, and antisocial personality disorder were not significant predictors of diagnosis stability and were dropped from subsequent analyses.

Two models were computed—a full logistic regression and a stepwise regression (using default parameters)—using all the variables found to be significant in the univariate analyses and corrected for center effects. Both models agreed that the severity of lifetime dependence index was the most important predictor variable and that the only other significant clinical predictors were

Table 3. Five-Year Stability of Lifetime Alcohol Dependence Diagnosis in Treated and Untreated* Individuals

Subject Group	Sex	*DSM-III-R* Initially Diagnosed, No.	*DSM-III-R* Same Diagnosis After 5 y, No. (%)	Feighner Definite Initially Diagnosed, No.	Feighner Definite Same Diagnosis After 5 y, No. (%)	COGA† Initially Diagnosed, No.	COGA† Same Diagnosis After 5 y, No. (%)	*DSM-IV* Initially Diagnosed, No.	*DSM-IV* Same Diagnosis After 5 y, No. (%)	*ICD-10* Initially Diagnosed, No.	*ICD-10* Same Diagnosis After 5 y, No. (%)
Stability in Treated Individuals											
Probands	Female	168	152 (90.5)	168	153 (91.1)	168	150 (89.3)	167	131 (78.4)	156	116 (74.4)
	Male	473	448 (94.7)	473	449 (94.9)	473	441 (93.2)	458	389 (84.9)	439	366 (83.4)
Siblings	Female	88	79 (89.8)	87	75 (86.2)	87	71 (81.6)	74	57 (77.0)	66	50 (75.8)
	Male	126	113 (89.7)	127	115 (90.6)	124	107 (86.3)	114	86 (75.4)	103	74 (71.8)
Controls	Female	2	2 (100.0)	2	2 (100.0)	2	2 (100.0)	2	2 (100.0)	2	2 (100.0)
	Male	10	10 (100.0)	11	11 (100.0)	10	10 (100.0)	8	6 (75.0)	7	5 (71.4)
Stability in Untreated Individuals											
Probands	Female	0	NA	0	NA	0	NA	0	NA	0	NA
	Male	0	NA	0	NA	0	NA	0	NA	0	NA
Siblings	Female	173	116 (67.0)	177	120 (67.8)	139	86 (61.9)	118	54 (45.8)	59	27 (45.8)
	Male	170	118 (69.4)	168	121 (72.0)	141	95 (67.4)	106	47 (44.3)	56	30 (53.6)
Controls	Female	38	9 (23.7)	34	12 (35.3)	20	5 (25.0)	23	3 (13.0)	5	1 (20.0)
	Male	92	56 (60.9)	79	51 (64.6)	55	35 (63.6)	49	12 (24.5)	19	9 (47.4)

Abbreviations: COGA, Collaborative Study on the Genetics of Alcoholism; *ICD-10*, *International Classification of Diseases, 10th Revision*; NA, not applicable.
*Stability of various lifetime diagnoses of alcoholism stratified by whether the individual had reported any treatment (medical, counseling, 12-step program, etc) at the first interview.
†The COGA diagnosis for alcohol dependence requires an individual to satisfy both *DSM-III-R* alcohol dependence and Feighner definite alcoholism criteria.

sex and treatment. The full model resulted in a C statistic of 0.832 (reflecting that 83% of the time, the model gave a higher predictive value to a stable individual than to an unstable one, and that 0.3% of the time, the individuals received the same score). The stepwise model, using severity of illness, sex, and treatment as the only clinical predictors, resulted in a very similar C statistic of 0.825. **Table 4** lists the clinical variables with significant univariate predictive value and their associated values from the full regression model.

A logistic regression analysis was then performed using 37 individual alcoholism symptoms at baseline, race, sex, cohort, dependence on other substances, age at onset for the COGA diagnosis, and comorbid psychiatric conditions as predictors and was corrected for center effects. This produced a C statistic of 0.879. This value is almost certainly due to overfitting, but it provides an upper limit for the stability information contained in these data. The simple model involving just severity index, sex, and treatment captured this information very well.

Table 4. Predictive Factors for Stability of the COGA Diagnosis of Alcohol Dependence: Multivariate Logistic Regression Results on Variables Significant in Univariate Analyses*

Variable		Odds Ratio (95% CI)	*P*
Symptom count	Low (3-4)	1.00	NA
	Moderate (5-6)	2.90 (1.86-4.52)	<.001
	High (7-8)	7.51 (4.30-13.13)	<.001
	Maximum (9)	16.10 (7.46-34.75)	<.001
Treatment	No	1.00	NA
	Yes	2.10 (1.37-3.21)	<.001
Sex	Female	1.00	NA
	Male	1.57 (1.07-2.32)	.02
Habitual smoking		1.13 (0.77-1.64)	.53
Marijuana dependence		1.11 (0.72-1.71)	.64
Cocaine dependence		0.82 (0.53-1.28)	.38
Other stimulant dependence		1.38 (0.74-2.59)	.31
Sedative dependence		1.52 (0.66-3.47)	.32
Opioid dependence		1.20 (0.56-2.58)	.64
Major depressive disorder		0.99 (0.90-1.09)	.82

Abbreviations: CI, confidence interval; COGA, Collaborative Study on the Genetics of Alcoholism; NA, not applicable.
*Data consisted of 641 probands and 491 siblings diagnosed with COGA alcoholism at the initial assessment (N = 1132). Results are from the multivariate regression model using clinical covariates found significant in univariate analyses (C = 0.832). Stepwise regression with default parameters retained only the severity variables (symptom counts), treatment, and sex. All results were corrected for COGA centers. All subjects with COGA alcohol dependence had a symptom count of at least 3.

STABILITY OF OTHER SUBSTANCE DEPENDENCE AND HABITUAL SMOKING

The comparative stability of other drug dependence and habitual smoking in relation to that observed for alcohol dependence was of interest. To this end, the stabilities of a lifetime history of habitual smoking and *DSM-III-R* diagnoses of other drug dependence were examined (**Table 5**). As before, stability was defined as the percentage of individuals diagnosed at the initial interview who were independently assigned the disorder at reassessment. Habitual smoking was the most stable classification over a 5-year period. Of the 965 individuals who reported a lifetime history of habitual smoking, approximately 96% reconfirmed this history after 5 years. No differences were seen across sex or among COGA probands, siblings, and controls.

Table 5. Stability of *DSM-III-R* Lifetime Diagnoses of Drug Dependence and Habitual Smoking

		Marijuana		Cocaine		Other Stimulants		Sedatives		Opioids		Habitual Smoking	
Subject Group	Sex	Initially Diagnosed, No.	Same Diagnosis After 5 y, No. (%)	Initially Diagnosed, No.	Same Diagnosis After 5 y, No. (%)	Initially Diagnosed, No.	Same Diagnosis After 5 y, No. (%)	Initially Diagnosed, No.	Same Diagnosis After 5 y, No. (%)	Initially Diagnosed, No.	Same Diagnosis After 5 y, No. (%)	Initially Diagnosed, No.	Same Diagnosis After 5 y, No. (%)
Probands	Female	67	42 (62.7)	87	65 (74.7)	42	25 (59.5)	25	6 (24.0)	27	16 (59.3)	92	92 (100.0)
	Male	221	156 (70.6)	220	171 (77.7)	120	81 (67.5)	83	31 (37.4)	78	38 (48.7)	299	286 (95.6)
Siblings	Female	97	52 (53.6)	106	69 (65.1)	45	22 (48.9)	38	14 (36.8)	24	13 (54.2)	246	234 (95.1)
	Male	149	100 (67.1)	98	73 (74.5)	51	29 (56.9)	28	7 (25.0)	35	24 (68.6)	197	190 (96.4)
Controls	Female	16	7 (43.8)	4	3 (75.0)	2	0 (0.0)	1	0 (0.0)	0	NA	54	52 (96.3)
	Male	29	23 (79.3)	8	7 (87.5)	3	1 (33.3)	2	0 (0.0)	1	0 (0.0)	77	72 (93.5)
Overall		579	380 (65.6)	523	388 (74.2)	263	158 (60.1)	177	58 (32.8)	165	91 (55.2)	965	926 (96.0)

Abbreviation: NA, not applicable.

Other substance dependence diagnoses had markedly varying degrees of stability. The overall stability is moderate for marijuana (66%, N=579), cocaine (74%, N=523), other stimulant (60%, N=263), and opioid (55%, N=165) dependence. There was less variation of stability across sex and between groups with drug dependence disorders than of that observed for alcohol dependence. However, as was found for alcohol dependence, most disorders were more stable in men than in women (eg, in siblings, the male vs female stability rates were marijuana 67.1% vs 53.6%, cocaine 74.5% vs 65.1%, other stimulants 56.9% vs 48.9%, and opioids 68.6% vs 54.2%, respectively). Only sedative dependence had low overall stability of lifetime diagnosis over the 5-year period (33%, N=177).

COMMENT

A lifetime history of alcohol dependence is a stable psychiatric diagnosis that can be reliably reproduced in interviews separated by 5 years. These findings are consistent with previous reports from other longitudinal studies of alcohol dependent individuals from the National Institute of Mental Health Collaborative Depression Program (N=196),[3] St Louis Epidemiologic Catchment Area study (N=31),[11] and the Vietnam era veterans (N=75).[13] Prospective studies on the clinical course of alcoholism, including studies of heavy drinkers in New Jersey (N=876),[20,21] sons of alcoholic subjects (N=435),[22,23] and the COGA subjects (N=298),[12] provide further support for the stability of an alcohol dependence diagnosis. In particular, in the Collaborative Depression Program, alcoholism was found to be a more stable diagnosis than any of the other lifetime psychiatric disorders analyzed, including major depression, mania, hypomania, schizophrenia, phobic disorder, antisocial personality disorder, and obsessive-compulsive disorder.[3]

The stability of the diagnosis of alcoholism does differ according to the classification system used. More stringent definitions of alcoholism are less likely to be stable. However, individuals satisfying a more stringent definition of alcoholism at first interview are more likely than others to receive a lifetime diagnosis of alcoholism under at least 1 of the definitions at reinterview. One way to reconcile these seemingly contrary observations is through a target shooting analogy. The alcohol dependence diagnoses examined here are close to being nested and can be visualized as concentric circles forming a target. The repeated assessments can be thought of as shooting twice at the target. While an individual who hits the bull's-eye (ie, *ICD-10*) on the first try may not hit the bull's-eye on a second try, the second shot is nonetheless more likely to hit the target than is a shot from someone who was far from the center of the target initially.

An extremely important point is that the likelihood of an individual diagnosis of alcoholism remaining stable depends greatly on the severity of illness. Thus, since distinct subject populations may have different degrees of severity of illness, the stability of the diagnosis of alcoholism may differ among samples. Reclassification of alcohol dependence at 2 time points was very reliable in the probands, all of whom were recruited from centers that treat alcoholism. In contrast, the classification of alcoholism in the community-based control group was much less stable. Our data suggest that the characteristic that most contributes to this stability is severity of illness. The difference in stability between these groups can be largely attributed to the fact that individuals in treatment tend to be more severely afflicted than the community-based control subjects. Evidence supporting this includes additional analyses showing that severity (whether defined by high symptom counts, treatment, or *ICD-10* diagnosis of alcoholism) strongly contributes to the stability of the diagnosis of alcoholism. In addition, siblings who have received treatment for alcoholism display stability for diagnoses of alcohol dependence similar to the stability in index cases.

Though subjects were recruited as part of a family study on alcohol dependence, this data set contains information on a large collection of individuals with other substance dependence. As a result, the COGA data provide a unique opportunity to compare stability of diagnoses across many drugs of abuse. In terms of other substances, history of habitual smoking was the most stable phenotype, with 96.0% of habitual smokers maintaining this classification at follow-up. There were no differences in stability across the different subject groups or by sex. Factors that may contribute to the stability of

habitual smoking are that it is simply defined, that there is little stigma attached to smoking (and virtually none for having been a past smoker), and that the criteria are broader than those used to define dependence for other substances. Additionally, smoking at least 1 pack of cigarettes per day for at least 6 months or more may represent a "severe" classification of smoking and so is reliably reported over long periods of time.

In contrast, stability of lifetime diagnosis for other substance dependence (marijuana, cocaine, other stimulants, and opioids) is moderate (range, 55%-74%) and slightly lower than that which was observed for the different definitions of alcoholism. As noted in the study of alcohol dependence, sex differences in stability are seen, with men more reliably reporting a lifetime history of drug dependence diagnoses over a long period of time compared with women. One striking exception in stability for other substance dependence was observed: stability for the *DSM-III-R* definition of sedative dependence was poor (33%). Sedative dependence is often associated with misuse of prescription drugs, such as diazepam and others, and the difficult differentiation between prescribed use and abuse over a long period of time (not required with alcohol, marijuana, and cocaine use) may contribute to lower stability.

The stability of diagnosis over time is an important characteristic in both clinical practice and research design. Clinically, it is important for health care providers to understand the reliability of measurement over time. For instance, given a history of alcohol dependence (even a remote history), caution is advised in the prescription of potentially addictive substances such as benzodiazepines and opiates. A history of alcohol dependence also alerts a physician to monitor for potential relapse. The most reliably reported history of alcohol dependence over a 5-year period is seen in the most severe cases and in those who have received treatment.

Since individuals with stable lifetime diagnoses are more likely to be true cases,[24] these results have implications for clinical and biological studies. In research design, misclassification will lead to less pure groups for analysis, ultimately resulting in a reduction in the power to find meaningful differences between the groups.[25] Great care is taken to define cases in clinical studies, and the results reported here indicate the importance of sampling severe cases. An efficient method of selecting severely affected individuals is to sample from treatment centers; individuals in the general population who satisfy criteria for substance dependence are more likely to be mildly affected, and thus less stable, cases. As a result, community-based samples, unless specifically recruited from severe cases, may not be appropriate for biological studies that require stable cases of alcohol dependence. This also has implications for those who develop health policy and treatment recommendations. For instance, examination of individuals with severe illness (such as those in treatment centers) can be expected to reveal recovery rates dramatically different from the recovery rates reported in general population samples. In part, the spontaneous recovery among the alcohol-dependent subjects in the general population may represent issues of misclassification of mild cases of alcoholism.

This study has several strengths and limitations. The COGA study is large, with comprehensive assessments separated over a 5-year time span. This presents an opportunity, thus far unique, to examine not only alcoholism, but also to expand the examination to smoking and other drug dependencies. Extensive quality assurance protocols were established in this project and special care was taken to assess subjects uniformly within and across sites.

One limitation is in the inability of these data to identify where the error in unstable cases occurred. Although it is clear that an error occurred in classification whenever an individual with a lifetime diagnosis of dependence on first interview does not receive the same diagnosis on reinterview, the specific error (either a false-positive diagnosis at initial assessment or a missed diagnosis at reassessment) is impossible to determine from this data. Faulty recall by interview subjects may be a factor degrading the stability of lifetime diagnoses.

There are several cautions that must be noted in the examination of drug dependence. First, the recruitment criteria excluded index cases with significant intravenous drug use. This exclusionary criterion has the effect of reducing opioid dependence in the index cases and possibly biasing the estimates of stability. However, it is important to note that siblings were recruited regardless of their intravenous drug use, and any potential bias should be greatly attenuated in this group. Second, the examination of the stability of drug dependence is not as extensive as it is for alcohol dependence.

Finally, a possible criticism of this study is that interviews were conducted by lay interviewers instead of physicians. Though the lay interviewers were college graduates (generally with a psychology major) who underwent weeks of training to perform this assessment, the question remains whether the estimated stability rates would have been markedly different had the evaluations been performed by clinicians.

In summary, in a population of treated individuals, alcohol dependence was a highly stable lifetime diagnosis, with stability as great or greater than that reported in other psychiatric illnesses such as major depression, bipolar illness, and schizophrenia. With the exception of sedative dependence, dependence on other substances and habitual smoking also displayed good stability in both alcohol-dependent probands and their siblings. The stability over a 5-year period adds to the confidence that researchers and clinicians have in the validity of the diagnosis and the classification system used. The clearest marker for stability in alcohol dependence is severity of the illness.

Submitted for Publication: May 25, 2004; final revision received November 16, 2004; accepted December 16, 2004.
Author Affiliations: Departments of Internal Medicine (Dr Culverhouse), Psychiatry (Drs Bucholz, Reich, and Bierut), and Genetics (Dr Reich), Washington University in St Louis School of Medicine, St Louis, Mo; University of Iowa College of Medicine, Iowa City (Dr Crowe); Department of Psychiatry, University of Connecticut, Farmington (Dr Hesselbrock); Department of Psychia-

try, Indiana University Medical Center, Indianapolis (Dr Nurnberger); Department of Psychiatry, State University of New York Health Sciences Center, Brooklyn (Dr Porjesz); Department of Psychiatry, University of California, San Diego (Dr Schuckit).

Correspondence: Robert Culverhouse, PhD, Department of Internal Medicine, Box 8005, Washington University in St Louis School of Medicine, 660 South Euclid Ave, St Louis, MO 63110-1026 (rob@ilya.wustl.edu).

Funding/Support: This work was supported in part by National Institutes of Health grants NIMH MH14677, NIDA DA13423, and NCI CA89392, and by funds from the Barnes-Jewish Hospital Foundation. This national collaborative study is supported by the National Institutes of Health Grant U10AA08403 from the National Institute on Alcohol Abuse and Alcoholism.

Acknowledgment: The Collaborative Study on the Genetics of Alcoholism (COGA) (principal investigator: H. Begleiter; coprincipal investigators: L. Bierut, H. Edenberg, V. Hesselbrock, B. Porjesz) includes 9 different centers where data collection, analysis, and storage take place. The 9 sites and principal investigators and coinvestigators are as follows: University of Connecticut, Farmington (V. Hesselbrock); Indiana University, Indianapolis (H. Edenberg, J. Nurnberger, Jr, P. M. Conneally, and T. Foroud); University of Iowa, Iowa City (R. Crowe and S. Kuperman); State University of New York Health Sciences Center, Brooklyn (B. Porjesz and H. Begleiter); Washington University in St Louis, St Louis, Mo (L. Bierut, J. Rice, and A. Goate); University of California, San Diego (M. Schuckit); Howard University, Washington, DC (R. Taylor); Rutgers University, Piscataway, NJ (J. Tischfield); and Southwest Foundation, San Antonio, Tex (L. Almasy). Lisa Neuhold serves as the National Institute on Alcohol Abuse and Alcoholism staff collaborator.

In memory of Theodore Reich, MD, coprincipal investigator of the Collaborative Study on the Genetics of Alcoholism since its inception and one of the founders of modern psychiatric genetics, we acknowledge his immeasurable and fundamental scientific contributions to the COGA and the field.

REFERENCES

1. Robins E, Guze SB. Establishment of diagnostic validity in psychiatric illness: its application to schizophrenia. *Am J Psychiatry*. 1970;126:983-987.
2. Feighner JP, Robins E, Guze SB, Woodruff RA Jr, Winokur G, Munoz R. Diagnostic criteria for use in psychiatric research. *Arch Gen Psychiatry*. 1972;26:57-63.
3. Rice JP, Rochberg N, Endicott J, Lavori PW, Miller C. Stability of psychiatric diagnoses: an application to the affective disorders. *Arch Gen Psychiatry*. 1992;49:824-830.
4. Rice JP, McDonald-Scott P, Endicott J, Coryell W, Grove WM, Keller MB, Altis D. The stability of diagnosis with an application to bipolar II disorder. *Psychiatry Res*. 1986;19:285-296.
5. Bucholz KK, Hesselbrock VM, Shayka JJ, Nurnberger JI Jr, Schuckit MA, Schmidt I, Reich T. Reliability of individual diagnostic criterion items for psychoactive substance dependence and the impact on diagnosis. *J Stud Alcohol*. 1995;56:500-505.
6. Hasin DS, Trautman KD, Miele GM, Samet S, Smith M, Endicott J. Psychiatric Research Interview for Substance and Mental Disorders (PRISM): reliability for substance abusers. *Am J Psychiatry*. 1996;153:1195-1201.
7. Hasin D, Carpenter KM, McCloud S, Smith M, Grant BF. The alcohol use disorder and associated disabilities interview schedule (AUDADIS): reliability of alcohol and drug modules in a clinical sample. *Drug Alcohol Depend*. 1997;44:133-141.
8. Grant BF, Harford TC, Dawson DA, Chou PS, Pickering RP. The Alcohol Use Disorder and Associated Disabilities Interview schedule (AUDADIS): reliability of alcohol and drug modules in a general population sample. *Drug Alcohol Depend*. 1995;39:37-44.
9. Canino G, Bravo M, Ramirez R, Febo VE, Rubio-Stipec M, Fernandez RL, Hasin D. The Spanish Alcohol Use Disorder and Associated Disabilities Interview Schedule (AUDADIS): reliability and concordance with clinical diagnoses in a Hispanic population. *J Stud Alcohol*. 1999;60:790-799.
10. Chatterji S, Saunders JB, Vrasti R, Grant BF, Hasin D, Mager D. Reliability of the alcohol and drug modules of the Alcohol Use Disorder and Associated Disabilities Interview Schedule–Alcohol/Drug-Revised (AUDADIS-ADR): an international comparison. *Drug Alcohol Depend*. 1997;47:171-185.
11. DeMallie DA, Cottler LB, Compton WM III. Alcohol abuse and dependence: consistency in reporting of symptoms over ten years. *Addiction*. 1995;90:615-625.
12. Schuckit MA, Smith TL, Danko GP, Bucholz KK, Reich T, Bierut L. Five-year clinical course associated with DSM-IV alcohol abuse or dependence in a large group of men and women. *Am J Psychiatry*. 2001;158:1084-1090.
13. Slutske WS, True WR, Scherrer JF, Goldberg J, Bucholz KK, Heath AC, Henderson WG, Eisen SA, Lyons MJ, Tsuang MT. Long-term reliability and validity of alcoholism diagnoses and symptoms in a large national telephone interview survey. *Alcohol Clin Exp Res*. 1998;22:553-558.
14. Bucholz KK, Cadoret R, Cloninger CR, Dinwiddie SH, Hesselbrock VM, Nurnberger JI Jr, Reich T, Schmidt I, Schuckit MA. A new, semi-structured psychiatric interview for use in genetic linkage studies: a report on the reliability of the SSAGA. *J Stud Alcohol*. 1994;55:149-158.
15. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R), Revised Third Edition*. Washington, DC: American Psychiatric Association; 1987.
16. Hesselbrock M, Easton C, Bucholz KK, Schuckit M, Hesselbrock V. A validity study of the SSAGA–a comparison with the SCAN. *Addiction*. 1999;94:1361-1370.
17. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), Fourth Edition*. Washington, DC: American Psychiatric Association; 1994.
18. World Health Organization. *International Classification of Diseases, 10th Revision (ICD-10)*. Geneva, Switzerland: World Health Organization; 1992.
19. SAS release 6.11. Cary, NC: SAS Institute; 1995.
20. Hasin D, Van Rossem R, McCloud S, Endicott J. Alcohol dependence and abuse diagnoses: validity in community sample heavy drinkers. *Alcohol Clin Exp Res*. 1997;21:213-219.
21. Hasin DS, Van Rossem R, McCloud S, Endicott J. Differentiating DSM-IV alcohol dependence and abuse by course: community heavy drinkers. *J Subst Abuse*. 1997;9:127-135.
22. Schuckit MA, Smith TL, Landi NA. The 5-year clinical course of high-functioning men with DSM-IV alcohol abuse or dependence. *Am J Psychiatry*. 2000;157:2028-2035.
23. Schuckit MA, Smith TL. An 8-year follow-up of 450 sons of alcoholic and control subjects. *Arch Gen Psychiatry*. 1996;53:202-210.
24. Maziade M, Roy MA, Fournier JP, Cliche D, Merette C, Caron C, Garneau Y, Montgrain N, Shriqui C, Dion C. Reliability of best-estimate diagnosis in genetic linkage studies of major psychoses: results from the Quebec pedigree studies. *Am J Psychiatry*. 1992;149:1674-1686.
25. Rothman KJ. *Modern Epidemiology*. Boston, Mass: Little, Brown & Co; 1986.