

Familial Transmission of Substance Use Disorders

Kathleen R. Merikangas, PhD; Marilyn Stolar, MA; Denise E. Stevens, PhD;
Joseph Goulet, MS; Martin A. Preisig, MD; Brenda Fenton, PhD; Heping Zhang, PhD;
Stephanie S. O'Malley, PhD; Bruce J. Rounsaville, MD

Background: There is increasing evidence that substance use disorders are familial and that genetic factors explain a substantial degree of their familial aggregation. To perform a controlled family study of probands with several different predominant drugs of abuse, including opioids, cocaine, cannabis, and/or alcohol.

Methods: The subjects for the present study included 231 probands with dependence on opioids, cocaine, cannabis, and/or alcohol and 61 control probands, and their 1267 adult first-degree relatives. Diagnostic estimates were based on semistructured diagnostic interviews and/or structured family history interviews regarding each proband, spouse, and adult first-degree relative. The interview data were reviewed blindly and independently by clinicians with extensive experience in the evaluation and treatment of substance use disorders.

Results: There was an 8-fold increased risk of drug disorders among the relatives of probands with drug disorders across a wide range of specific substances, including opioids, cocaine, cannabis, and alcohol, which is largely independent from the familial aggregation of both alcoholism and antisocial personality disorder. There was also evidence of specificity of familial aggregation of the predominant drug of abuse.

Conclusions: Elevation in risk of this magnitude places a family history of drug disorder as one of the most potent risk factors for the development of drug disorders. These results suggest that there may be risk factors that are specific to particular classes of drugs as well as risk factors that underlie substance disorders in general.

Arch Gen Psychiatry. 1998;55:973-979

THE FAMILIAL aggregation of alcoholism has been well established.^{1,2} Although the results of numerous studies suggest that drug abuse is familial, there is a lack of adequate evidence from studies that use contemporary family study methods, including comparable control probands and direct interviews of relatives, in investigating the familial patterns of drug abuse.³⁻¹⁴

*See also pages 964, 967,
and 982*

Although most twin studies of substance abuse have focused on alcoholism, an increasing number have investigated twin concordance for drug use and abuse.^{9-11,15-19} In fact, several studies have found greater levels of heritability for drug abuse than for alcoholism.¹⁸ Studies of twin registries have demonstrated the importance of genetic factors in both the quantity and frequency of use and degree of abuse of specific drugs, including nicotine, caffeine, tran-

quilizers, and sedatives.^{9-11,18} Results of a recent large-scale twin study of male Vietnam-era veterans suggest that substance abuse is highly heritable, and that the contribution of genetic factors is more significant for frequent use or abuse than for nonproblematic use.¹⁷ Of particular interest was the finding that the subjective effects of marijuana, including suspiciousness and agitation, are also under genetic control.¹⁹ Likewise, the classic adoption studies of Cadoret et al²⁰⁻²³ provide further evidence of the importance of the role of genetic factors in the development of drug disorders, with a far greater impact on the transition from drug use to abuse than on drug use itself.

The present study was designed to investigate the familial aggregation of drug and alcohol disorders across a broad range of drugs, including opioids, cocaine, mari-

*This article is also available on our
Web site: www.ama-assn.org/psych.*

From the Departments of Epidemiology and Public Health (Drs Merikangas, Stevens, and Zhang, Ms Stolar, and Mr Goulet) and Psychiatry (Drs Merikangas, O'Malley, and Rounsaville), Yale University School of Medicine, New Haven, Conn; Department of Psychiatry, University of Lausanne, Lausanne, Switzerland (Dr Preisig); and Department of Psychiatry, University of Geneva, Geneva, Switzerland (Dr Fenton).

SUBJECTS AND METHODS

SAMPLE CHARACTERISTICS

Probands

The sample of 299 probands was composed of a total of 149 probands with drug dependence (87 probands with opioid, 27 probands with cocaine, and 35 probands with cannabis dependence) and 89 probands with alcohol dependence, recruited from outpatient specialty clinics for substance disorders, and 61 control probands with no evidence of a lifetime history of any diagnosis in *DSM-III-R*.²⁴ The controls were recruited through a random-digit dialing procedure in the greater New Haven, Conn, area. Study criteria were presented in detail by Merikangas et al.²⁵

Relatives

There were a total of 1267 first-degree relatives, primarily composed of parents and siblings (42% parents, 51% siblings, and 7% offspring). Overall, 57% of the relatives of probands who met study criteria were interviewed directly, either in person or by telephone (approximately 25% of the total number of relatives). Twenty percent of the first-degree relatives who refused direct interviews were assessed via informant reports. The interview rates did not significantly differ by proband diagnostic group and are in accordance with previous family studies of substance abuse.^{3,4,13}

OVERVIEW OF PROCEDURES

The procedures of the current study included the following: (1) interviewers with experience in substance abuse or clinical psychiatry interviewed relatives blindly with respect to the disorder of the index family member; (2) direct semistructured diagnostic interviews were applied, with expanded information on the correlates and course of patterns of drug use, particularly with respect to polysubstance use and abuse; (3) semistructured informant interviews were used, with expanded sections on substance abuse to obtain family history information; and (4) standardized diagnostic criteria based on information from both clinical material and informant reports were used in conjunction with the direct interview to assess diagnostic criteria for substance disorders and other psychiatric disorders (ie, best-estimate diagnoses).

Diagnostic Interview

The diagnostic interview for adults was the semistructured Schedule for Affective Disorders and Schizophrenia, current and lifetime versions,²⁶ modified to obtain *DSM-III*²⁷ and *DSM-III-R*²⁴ criteria. With respect to substance abuse, the interview was modified to obtain more detailed information on the patterns of use of each drug class and their interrelationship, and on the course of alcohol and drug use and abuse.

Kappas derived from joint ratings of individual interviews were generally quite high for substance abuse (0.72-0.94) and somewhat lower for anxiety or affective disorders (0.54-0.78) across the first 3 series of training sessions. Comparison of diagnoses obtained through direct face-to-face interview and those from telephone interviews in both the present study and previous studies²⁸⁻³¹ showed high levels of agreement across all diagnostic categories.

Family History Information

Family history information was obtained by means of a modified version of the Family History-Research Diagnostic Criteria developed by Andreasen et al³² for data collected by the family history method designed to obtain both *DSM-III* and *DSM-III-R* diagnoses in adults and children. The family history interview was modified to obtain more extensive information on patterns and sequelae of drug and alcohol use as well as extent of knowledge by the informant about the index subject.

Diagnostic Procedures

The probands were assigned to the 5 lifetime diagnostic substance disorder groups based on the predominant type of substance disorder through a blind and independent review by clinicians with extensive experience in the evaluation and treatment of substance abuse (K.R.M., S.S.O., B.J.R.). The predominant substance of abuse of probands and relatives was determined through a review of the following information on the life chart of substance use based on the diagnostic interview, treatment records where relevant, and family history information: age at onset, order of onset, quantity, frequency, chronicity, substance of choice, number of symptoms, and severity.

Statistical Analysis

To assess the demographic homogeneity of the proband groups and their relatives, χ^2 tests for contingency tables with discrete demographic variables and 1-way analyses of variance for continuous measures were applied.

To account for familial clustering, mixed-effects multinomial logistic regression models were run with a program called MIXNO.³³ MIXNO provides maximum marginal likelihood estimates of parameters for mixed-effects logistic regression of correlated nominal response data. In the present analyses, mixed-effects multinomial logistic regression models were used to investigate the association between (1) a 3-level substance disorder diagnosis variable (drug dependence \pm alcohol dependence; alcohol dependence only; neither) in probands and relatives and (2) a 4-level predominant drug disorder variable (opioid, cocaine, cannabis, none) in probands (independent variable) and relatives (dependent variable), while adjusting for model covariates and correlated within family observations across all outcomes.

juana, and alcohol. Specifically, we examined the following patterns of familial associations: (1) the association between substance disorders in probands and relatives (ie, familial aggregation); (2) the association between drug dis-

orders in probands and alcoholism in relatives and vice versa (ie, independence); and (3) the association between the predominant drug disorder in probands and relatives (ie, specificity).

Table 1. Demographic Distribution of Probands and Relatives

	Predominant Drug Disorder in Probands					Test for Homogeneity of Percentages or Means, <i>P</i>
	Opioid (n = 87)	Cocaine (n = 27)	Cannabis (n = 35)	Alcohol (n = 89)	Controls (n = 61)	
Probands (n = 299)						
Sex, % male	37	41	60	71	43	$\chi^2_4 = 24.966, <.001$
Mean \pm SD age, y	35.3 \pm 5.3*	34.1 \pm 5.1*	35.9 \pm 4.2*	40.4 \pm 6.7	40.8 \pm 5.9	$F_{4,294} = 16.20, <.001$
Socioeconomic status, Hollingshead Score >III, %	82	77	61	53	25	$\chi^2_4 = 49.211, <.001$
Marital status, married or remarried, %	39	44	63	60	97	$\chi^2_4 = 53.071, <.001$
Relatives (n = 1267)						
No.	332	94	178	408	255	
Sex, % male	49	50	50	51	49	$\chi^2_4 = 0.225, .99$
Mean \pm SD age, y	49.2 \pm 17.3	50.1 \pm 17.4	45.8 \pm 15.8*	49.0 \pm 17.3	50.1 \pm 18.7	$F_{4,1262} = 1.81, .13$

*Dunnett t test, *df* = 1; adjusted *P* < .05 for significant difference from controls.

RESULTS

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF PROBANDS AND RELATIVES

Demographic characteristics of probands and relatives are presented in **Table 1**. Although the sex and age composition of the drug-abusing probands differed from that of the controls, there were no statistically significant differences in the age and sex distribution of the relatives.

There were no significant differences in the mean number of relatives of probands when compared with controls (ie, 4.5 relatives per proband). Of the 1267 first-degree biological relatives, 42% were parents, 51% were siblings, and 7% were offspring older than 18 years.

FAMILIAL AGGREGATION OF ALCOHOLISM AND DRUG DISORDERS

The familial aggregation of alcoholism and drug disorders is presented in **Table 2** and **Table 3**. Table 2 presents the proportions of substance use disorders across broad categories of drugs, including "hard" drugs (ie, opioids, cocaine, stimulants, hallucinogens, or inhalants), "soft" drugs (ie, cannabis, sedatives, benzodiazepines, or barbiturates), alcohol, and nicotine among relatives by the predominant drug disorder of probands. Rates of hard drug disorders increased according to the deviance of the predominant drug among probands. Rates of abuse or dependence on hard drugs were greatest among the relatives of probands with opioid disorders (14.5%), moderately elevated among relatives with cocaine or cannabis disorders (9.6% or 8.4%, respectively), and lowest among relatives of probands with alcoholism (4.4%) when compared with relatives of controls (1.2%). In contrast, rates of alcoholism were increased only among the relatives of probands with cannabis or alcohol dependence compared with those of either the opioid or cocaine groups or the controls. Finally, rates of nicotine dependence were elevated among the relatives of all of the substance use disorder proband groups compared with those of controls. Approximately two thirds of the relatives reported a history of dependence on nicotine.

Table 3 presents the proportions of relatives with drug and/or alcohol disorders according to the presence or absence of drug and alcohol disorders in probands. The main effects of the familial aggregation of all alcoholism and drug disorders were highly significant: the relatives of probands with drug disorders had a 4.5-fold greater rate of drug disorders themselves than relatives of controls. Likewise, relatives of probands with alcohol disorders had a 2.0-fold greater rate of alcohol disorders than relatives of controls.

Statistically significant pairwise differences of proportions and their respective SEs, *z* scores, and *P* values are shown in the footnotes to Table 3. The proportions of relatives with both drug and alcohol disorders did not differ between those of probands with pure drug disorders (8.1%) and relatives of probands with comorbid drug disorders and alcohol disorders (9.1%). The lack of differences between rates of drug disorders among relatives of probands with comorbid drug disorders and alcoholism compared with relatives of probands with drug disorders only suggests that alcoholism and drug disorders are independent and that comorbidity is not an indicator of severity of substance disorders in probands.

Likewise, no significant evidence of coaggregation of pure forms of alcoholism and drug disorders emerged. Rates of pure drug disorders were increased among relatives of probands with pure drug disorders when compared with those of probands with alcohol only (*P* = .003); conversely, rates of pure alcoholism in the relatives were significantly elevated among relatives of probands with alcoholism only vs those with drug-only diagnoses (*P* < .001). Because similar patterns of familial aggregation of substance disorders emerged among relatives of probands in the drug and alcoholism group vs those in the drug-only group (see Table 3), these groups were collapsed in subsequent analyses.

Table 4 examines the association between drug and alcohol disorders in probands and relatives cross-classified according to the presence or absence of drug and alcohol disorders after controlling for demographic and clinical covariates. A mixed-effects generalized logit model, which allows for both adjustment for correlated observations (within families) and the simultaneous investigation of the 3 levels of the outcome variable (drug

Table 2. Proportions of Relatives With Drug Disorders by Predominant Substance in Probands

Proband Drug Disorder	Drug Disorders in Relatives, %*					
	No. of Relatives	"Hard" Drugs†	"Soft" Drugs‡	All Drugs	Alcohol	Nicotine
Opioid	332	14.5	11.5	20.5	14.5	68.1
Cocaine	94	9.6	8.5	14.9	18.1	78.3
Cannabis	178	8.4	18.5	21.3	36.0	60.0
Alcohol	408	4.4	7.1	8.3	35.5	61.2
Controls	255	1.2	3.5	3.5	14.9	44.1
Total	1267	7.3	9.2	12.9	24.6	60.7

*Categories are not mutually exclusive.
 †Opioids, cocaine, hallucinogens, inhalants.
 ‡Cannabis, sedatives, barbiturates.

Table 3. Alcoholism and Drug Abuse in Probands and Relatives

Probands	No. of Relatives	Relatives With Drug and Alcohol Disorders, %*			
		Drug and Alcohol†	Drug Only‡	Alcohol Only§	Neither
Drug and alcohol	431	9.1	9.1	15.0	66.8
Drug only	173	8.1	8.7	6.3	76.9
Alcohol only	408	7.8	2.0	27.7	62.5
Control	255	3.1	0.8	11.8	84.3

*For the proportion of relatives with the indicated disorders, statistically significant contrasts among proband groups, $\alpha = .05$; *P* values are not adjusted for multiple comparisons. Boldface cells indicate specificity of concordance between probands and relatives.
 †Drug and alcohol vs controls, percentage difference (% diff) = 6.0, SE = 1.8, $z = 3.36$, $P < .001$; alcohol vs controls, % diff = 4.7, SE = 1.7, $z = 2.73$, $P = .006$.
 ‡Drug and alcohol vs alcohol only, % diff = 7.1, SE = 1.5, $z = 4.60$, $P < .001$; drug and alcohol vs controls, % diff = 8.3, SE = 1.5, $z = 5.56$, $P < .001$; drug only vs alcohol only, % diff = 6.7, SE = 2.2, $z = 2.99$, $P = .003$; and drug only vs controls, % diff = 7.9, SE = 2.2, $z = 3.47$, $P < .001$.
 §Drug and alcohol vs drug only, % diff = 8.7, SE = 2.5, $z = 3.44$, $P < .001$; drug and alcohol vs alcohol only, % diff = -12.7, SE = 2.8, $z = -4.50$, $P < .001$; drug only vs alcohol only, % diff = -21.4, SE = 2.9, $z = -7.38$, $P < .001$; drug only vs controls, % diff = -5.5, SE = 2.7, $z = -1.97$, $P = .049$; and alcohol only vs controls, % diff = 15.9, SE = 3.0, $z = 5.32$, $P < .001$.

disorder with or without alcoholism; alcoholism alone; neither) was used. Applying the analyses presented in Table 4 to the subset of directly interviewed relatives yielded similar results. The intraclass correlations for familial clustering derived by the MIXNO program for nominal logistic regression analysis were 0.17 for alcoholism only vs none, and 0.04 for drug with or without alcoholism vs none.

After potential confounders were considered, these results were consistent with those in Table 3; alcoholism and drug disorders aggregated independently in families, since there was no effect modification of the association between drug disorders in probands and relatives by the presence of alcoholism in the proband, nor was the association between alcoholism in probands and relatives modified by the presence of drug disorders in the proband. The strongest association between proband and relatives' drug and/or alcohol disorders emerged for drug disorders with or without alcoholism in relatives of probands with drug disorders (adjusted odds ratio, 7.9). Likewise, there was a significant association between alcoholism only in probands and relatives (adjusted odds ratio, 4.2). Cross comparisons indicated that drug disorders in probands were associated with a significantly lower magnitude of alcoholism in relatives than that among relatives of probands with alcoholism only. Finally, there was also a significantly elevated odds ratio of drug disorders (with or without alcoholism) among the relatives of probands with alcoholism compared with those of control probands. Although this would appear to suggest a lack of specificity of the fa-

mily aggregation of drug and alcohol disorders, the elevation in this group of relatives was found to be most strongly attributable to comorbid alcohol and drug disorders rather than to drug disorders alone.

FAMILIAL PATTERNS OF SPECIFIC DRUGS

The association between rates of the predominant drug disorder in probands and relatives is shown in Table 5. The statistically significant differences in the proportions between the predominant drug disorder in probands and the same predominant drug disorder in relatives are presented in the footnotes to Table 5, along with test statistics and *P* values.

The results in Table 5 show that there was a strong association between the predominant drug disorder in probands and relatives. The rates shown on the diagonal exceed the off-diagonal rates of all of the drug disorders and alcoholism. Inspection of the *P* values of the *z* scores comparing rates of the predominant drug in probands and relatives vs other proband drug groups showed significant levels of specificity for opioids, cannabis, and alcohol, with a weaker trend toward specificity of cocaine. Similar trends emerged when this analysis was applied to the subset of directly interviewed relatives.

Table 6 presents the results of the mixed-effects generalized logit model of the associations between the predominant drug disorders in probands and relatives after controlling for the effects of relevant covariates. The results in Table 6 confirm the findings of a direct associa-

Table 4. Adjusted Odds Ratios of Drugs and Alcohol Disorders in Relatives by Proband Diagnostic Group

	Relatives: Adjusted Odds Ratio (95% Confidence Interval)	
	Drug ± Alcohol	Alcohol Only
Proband group		
Drug ± alcohol vs alcohol only	1.3 (0.9-2.2)	0.3 (0.2-0.6)*
Drug ± alcohol vs controls	7.9 (3.6-17.4)*	1.4 (0.8-2.5)
Alcohol only vs controls	6.0 (2.6-13.1)*	4.2 (2.3-5.7)*
Covariates		
Sex of proband, female vs male	2.0 (1.3-3.2)†	1.4 (0.9-2.1)
Antisocial in proband	0.8 (0.5-1.3)	1.4 (0.8-2.2)
Antisocial in relative	7.6 (4.1-14.0)*	2.4 (0.6-3.4)
Sex of relative, female vs male	0.4 (0.2-0.6)*	0.3 (0.2-0.5)*
Age of relative, <50 y vs >50 y	8.2 (4.8-14.5)*	0.8 (0.5-1.1)
Interview status	3.5 (2.2-5.7)*	1.9 (1.3-3.0)†

* $P < .001$.

† $P < .01$.

tion between the predominant drug disorders in probands and relatives reported in Table 5. For each of the specific drugs investigated, the adjusted odds ratio was greatest for the same drug disorder in the relatives (ie, 10.2 for opioids, 4.4 for cocaine, and 5.8 for cannabis) compared with the cross-drug associations. However, the overlapping and wide confidence intervals in the specific vs cross-drug comparisons also suggest that specificity should be considered as a trend rather than a conclusive finding.

COMMENT

The results of the present study show a remarkable degree of familial aggregation of substance abuse. There was an 8-fold increased risk of drug disorders among relatives of probands with drug disorders across a wide range of specific substances, including opioids, cocaine, cannabis, and sedatives, compared with that of relatives of controls. Elevation in risk of this magnitude demonstrates that a family history of drug abuse is one of the most potent risk factors for the development of drug abuse.

The increased risk of both drug disorders and alcoholism in male relatives across all proband groups is in accordance with the sex ratio for these disorders reported in large-scale epidemiological studies.^{34,35} The results of the present study confirm those of previous family studies of alcoholism,^{36,37} concluding that genetic factors appear to operate similarly in men and women. With respect to drug disorders, however, the small number of female probands in most previous studies has diminished the power to detect sex differences.³⁷ For example, Pickens et al¹⁶ concluded that the lack of significance of heritability of drug abuse in female twins was attributable to the low number of female pairs, since the magnitude of increase in concordance rates between monozygotic and dizygotic twins was similar in male and female twin pairs. The adoption studies of Cadoret et al^{22,23} also demonstrated equivalent genetic pathways underlying substance abuse in males and females. The familial aggregation of drug disorders was greater among relatives of women than men in the pres-

ent study, suggesting greater familial loading among women. The greater tendency for assortative mating among female than male substance abusers is one possible explanation for this finding.³⁸

The familial aggregation of drug disorders was largely independent of that of both alcoholism and antisocial personality disorder, thereby confirming the results of previous family^{6,8,13,39} and twin studies that suggest independence of genetic factors predisposing to alcohol and drug disorders.^{15,18} In the present study there was no evidence of cross-transmission of drug disorders and alcoholism, nor did the presence of alcoholism modify the association between drug disorders in probands and relatives and vice versa.

The specificity of familial aggregation of the predominant drug disorder, particularly cannabis and alcohol, and to some extent the opioids, was unexpected. Several previous studies have shown a specific association between parental and offspring marijuana and nicotine use.^{7,40,41} Even more surprising in these earlier studies was the conclusion that parental and offspring resemblance was not attributable to direct exposure to parental substance use. These findings suggest that there may be some genes or environmental factors that predispose to the use of specific drugs rather than contributing to a deviant pattern of behavior or substance abuse in general.

In addition to some evidence for specificity of familial aggregation of the predominant drug disorder, the results also suggest that alcoholism and the specific drug disorders investigated herein appear to represent a continuum of severity. There was a direct increase in rates of serious drug disorders among relatives with increasing levels of "deviance" of substance disorders in probands ranging from alcoholism (4% drug disorders in relatives) to cannabis (8% in relatives) to cocaine (10% in relatives) to opioid abuse or dependence (15% in relatives) as compared with 1% among control relatives. Therefore, familial factors may be associated with increasing levels of progression along this continuum of severity of substance abuse rather than to the preference for a particular salient substance of abuse.

Familial clustering of drug abuse could be attributable to either common genetic or environmental factors that influence the development of drug disorders. Genetic factors could influence vulnerability to the development of drug abuse through individual differences in the effects of the drugs themselves, including metabolism, sensitivity, tolerance, side effects, and cognitive or psychological effects, or in alteration of affective, emotional, or cognitive states, such as reduction of stress, depression, or anxiety.^{42,43}

Families may convey an increased risk of substance disorders through both specific (eg, increasing environmental exposure to drugs or facilitating drug availability⁴⁴⁻⁴⁶) and nonspecific (eg, impaired parenting behavior, exposure to marital discord, acute or chronic stress, negative life events, disrupted family structure, social deprivation, and physical, sexual, and emotional abuse) mechanisms.⁴⁷⁻⁵⁶ However, most of these family factors are not specific to drug disorders, since they also have been shown to characterize families of individuals with alcoholism as well as other psychiatric disorders.

There are several unique aspects of the design and methods of the present study that enhance its contribu-

Table 5. Specific Drug Disorders in Proband and Relatives

Proband Drug Disorder	No. of Relatives	Predominant Drug Disorder in Relatives, %*				All Drugs
		Opioid†	Cocaine‡	Cannabis§	Alcohol	
Opioid	332	10.2	4.2	6.0	19.9	14.4
Cocaine	94	2.1	7.5	5.3	22.3	9.6
Cannabis	178	6.2	2.3	12.9	20.2	8.4
Alcohol	408	1.7	2.7	3.9	28.4	4.4
Controls	255	0.4	0.8	2.4	11.0	1.2

*For the proportion of relatives with the indicated specific drug disorder, statistically significant contrasts among proband groups, $\alpha = .05$; P values are not adjusted for multiple comparisons. Boldface cells indicate specificity of concordance between probands and relatives.
 †Opioid vs cocaine, percentage difference (% diff) = 8.1, SE = 2.2, z = 3.63, P < .001; opioid vs alcohol, % diff = 8.5, SE = 1.8, z = 4.78, P < .001; and opioid vs controls, % diff = 9.8, SE = 1.7, z = 5.76, P < .001.
 ‡Cocaine vs controls, % diff = 6.7, SE = 2.8, z = 3.93, P < .001.
 §Cannabis vs opioid, % diff = 6.9, SE = 2.8, z = 2.44, P = .02; cannabis vs cocaine, % diff = 7.6, SE = 3.4, z = 2.22, P = .03; cannabis vs alcohol, % diff = 9.0, SE = 2.7, z = 3.34, P < .001; and cannabis vs controls, % diff = 10.5, SE = 2.7, z = 3.93, P < .001.
 ||Alcohol vs opioid, % diff = 8.5, SE = 3.1, z = 2.73, P = .006; alcohol vs cannabis, % diff = 8.2, SE = 3.7, z = 2.19, P = .03; and alcohol vs controls, % diff = 17.4, SE = 3.0, z = 5.88, P < .001.

Table 6. Adjusted Odds Ratios for Associations Between Predominant Drug Disorder in Proband and Relatives

	Predominant Drug Disorders in Relatives, Adjusted Odds Ratio (95% Confidence Interval)*		
	Opioids (n = 55)	Cocaine (n = 38)	Cannabis (n = 70)
Predominant drug disorders in probands			
Opioids (n = 87)	10.2 (3.2-32.6)†	2.8 (1.1-7.2)‡	2.4 (1.1-5.9)‡
Cocaine (n = 27)	2.2 (0.3-15.8)	4.4 (1.5-13.2)§	1.8 (0.5-6.3)
Cannabis (n = 35)	8.2 (1.7-39.1)§	1.9 (0.4-8.5)	5.8 (2.6-12.9)†
Effects of confounders			
Antisocial personality in proband	0.4 (0.2-1.2)	0.5 (0.2-1.7)	1.0 (0.5-2.1)
Antisocial personality in relative	79.9 (26.9-237.4)†	7.0 (1.4-35.4)‡	7.4 (2.3-23.4)†
Sex of proband, female vs male	1.1 (0.4-3.0)	2.8 (1.1-7.0)‡	1.4 (0.7-2.6)
Sex of relative, female vs male	0.7 (0.3-1.7)	0.4 (0.1-0.9)‡	0.5 (0.3-0.9)‡
Age of relative, <50 y	8.1 (3.1-21.1)†	49.7 (2.9-86.1)§	12.1 (4.5-32.7)†
Interview status of relative	0.4 (0.1-1.7)	0.9 (0.3-3.1)	2.5 (1.3-4.7)§

*Boldface cells indicate specificity of concordance between probands and relatives.
 †P < .001.
 ‡P < .05.
 §P < .01.

tion to current knowledge regarding familial factors and drug disorders. Design features include (1) a control group in which similar diagnostic and assessment methods were used; (2) probands with a range of drugs of abuse that strengthens the generalizability of the results; (3) a sufficient number of female probands to allow investigation of familial patterns of substance abuse among women; and (4) application of a statistical method that examines multinomial classification of probands and relatives simultaneously while controlling for the effects of clustered observations in families.

Limitations include (1) the lack of direct interview data on some of the relatives, necessitating the derivation of best-estimate diagnoses from family history information; (2) the imprecision of retrospective data in characterization of patterns of drug use and abuse (particularly among polysubstance abusers); (3) the lack of power to test adequately patterns of cross-transmission of specific drugs with such low base rates; and (4) possible selection biases with respect to clinical sampling of probands and

recruitment of families with offspring, which may limit generalizability of the results.

Because the family has been shown to play a critical role in the etiology of drug use and abuse, it is important to obtain a deeper understanding of the complex mechanisms through which the family exerts its influence. Additional controlled family and twin studies are critical to identify patterns of expression of substance disorders and comorbid psychiatric disorders, to test the classic modes of genetic transmission of substance abuse, to determine the role of sex-specific patterns of transmission of substance abuse, and to elucidate the role of genetic and environmental factors and their interaction in its development.

Specificity of familial aggregation of some classes of drugs as well as independence from alcoholism suggests that research and treatment should focus on specific drugs of abuse and patterns of concurrent use to determine whether different genetic, biological, and environmental risk factors underlie their development.

In terms of prevention, these findings support a shift in drug prevention programs from the universal level to programs that target the families of substance abusers.

Accepted for publication May 26, 1998.

This work was supported primarily by grant DA05348 and in part by grants AA07080, AA09978, DA09055, and MH36197 and by Research Scientist Development Awards K02 DA00293 (Dr Merikangas) and K05 DA00059 (Dr Rounsaville) from the Alcohol, Drug Abuse and Mental Health Administration of the US Public Health Service; and by MH14235 training awards (Drs Stevens and Fenton, Mr Goulet, and Ms Stolar). The Swiss National Science Foundation (grant 8238-033242) provided support to Dr Preisig.

We thank Donald Hedeker, PhD, Division of Epidemiology and Biostatistics, School of Public Health, University of Illinois at Chicago, for making available to us his Fortran program MIXNO.

Reprints: Kathleen R. Merikangas, PhD, Genetic Epidemiology Research Unit, Yale University School of Medicine, 40 Temple St, New Haven, CT 06510 (e-mail: kathleen.merikangas@yale.edu).

REFERENCES

1. Merikangas KR. The genetic epidemiology of alcoholism. *Psychol Med*. 1990; 20:11-22.
2. McGue M. Genes, environment, and the etiology of alcoholism. In: Zucker R, Boyd G, Howard J, eds. *The Development of Alcohol Problems: Exploring the Biopsychosocial Matrix*. NIAAA Research Monograph No. 26. Rockville, Md: US Dept of Health and Human Services, Public Health Service, National Institutes of Health, National Institute on Alcohol Abuse and Alcoholism; 1994:1-39.
3. Croughan JL. The contributions of family studies to understanding drug abuse. In: Robins L, ed. *Studying Drug Abuse*. New Brunswick, NJ: Rutgers University Press; 1985:240-264.
4. Rounsaville BJ, Kosten TR, Weissman MM, Prusoff BA, Pauls D, Foley S, Merikangas KR. Psychiatric disorders in the relatives of probands with opiate addiction. *Arch Gen Psychiatry*. 1991;48:33-42.
5. Gordon HW. Human neuroscience at National Institute on Drug Abuse: implications for genetics research. *Am J Med Genet*. 1994;54:300-303.
6. Hill SH, Cloninger CR, Ayre FR. Independent familial transmission of alcoholism and opiate abuse. *Alcohol Clin Exp Res*. 1977;1:335-342.
7. Gfroerer J. Correlation between drug use by teenagers and drug use by older family members. *Am J Drug Alcohol Abuse*. 1987;13:95-108.
8. Meller W, Rinehart R, Cadoret R, Troughton E. Specific familial transmission in substance abuse. *Int J Addict*. 1988;23:1029-1039.
9. Claridge G, Ross E. Sedative drug tolerance in twins. In: Claridge G, Canter S, Hume W, eds. *Personality Differences and Biological Variations: A Study of Twins*. Oxford, England: Pergamon Press; 1978:115-131.
10. Pedersen N. Twin similarity for usage of common drugs. In: Greda L, Paris P, Nance W, eds. *Twin Research 3: Epidemiological and Clinical Studies*. New York, NY: Alan R Liss Inc; 1981:53-59.
11. Gurling H, Grant S, Dangi J. The genetic and cultural transmission of alcohol use, alcoholism, cigarette smoking and coffee drinking: a review and an example using a log linear cultural transmission model. *Br J Addict*. 1985;80:269-279.
12. Mirin S, Weiss R, Michael J. Psychopathology in substance abusers: diagnosis and treatment. *Am J Drug Alcohol Abuse*. 1988;14:139-157.
13. Mirin SM, Weiss RD, Griffin ML, Michael JL. Psychopathology in drug abusers and their families. *Compr Psychiatry*. 1991;32:36-51.
14. Merikangas KR, Rounsaville BJ, Prusoff BA. Familial factors in vulnerability to substance abuse. In: Glantz MD, Pickens RW, eds. *Vulnerability to Drug Abuse*. Washington, DC: American Psychological Association; 1992:75-98.
15. Grove W, Eckert E, Heston L, Bouchard T, Segal N, Lykken D. Heritability of substance abuse and antisocial behavior. *Biol Psychiatry*. 1990;27:1293-1304.
16. Pickens R, Svikis D, McGue M, Lykken D, Heston L, Clayton P. Heterogeneity in the inheritance of alcoholism. *Arch Gen Psychiatry*. 1991;48:19-28.
17. Tsuang MT, Lyons MJ, Eisen SA, Goldberg J, True W, Nang L, Meyer JM, Eaves L. Genetic influences on abuse of illicit drugs. *Am J Med Genet*. 1996;5:473-477.
18. Jang KL, Livesley WJ, Vernon PA. Alcohol and drug problems: a multivariate behavioural genetic analysis of co-morbidity. *Addiction*. 1995;90:1213-1221.
19. Lyons MJ, Toomey R, Meyer JM, Green AI, Eisen A, Goldberg J, True WR, Tsuang MT. How do genes influence marijuana use? the role of subjective effects. *Addiction*. 1997;92:409-417.
20. Cadoret R, Troughton E, O'Gorman T, Heywood E. An adoption study of genetic and environmental factors in drug abuse. *Arch Gen Psychiatry*. 1986;43:1131-1136.
21. Cadoret RJ. Genetic and environmental factors in initiation of drug use and the transition to abuse. In: Glantz M, Pickens R, eds. *Vulnerability to Drug Abuse*. Washington, DC: American Psychological Association; 1992:99-113.
22. Cadoret RJ, Yates WR, Troughton E, Woodworth G, Stewart MA. Adoption study demonstrating two genetic pathways to drug abuse. *Arch Gen Psychiatry*. 1995; 52:42-52.
23. Cadoret RJ, Yates WR, Troughton E, Woodworth G, Stewart MA. An adoption study of drug abuse/dependency in females. *Compr Psychiatry*. 1996;37:88-94.
24. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised*. Washington, DC: American Psychiatric Association; 1987.
25. Merikangas KS, Stevens D, Fenton B, O'Malley S, Woods S, Stolar M, Risch M. Comorbidity of alcoholism and anxiety disorders. *Psychol Med*. In press.
26. Endicott J, Spitzer R. A diagnostic interview: the Schedule for Affective Disorders and Schizophrenia-Lifetime version. *Arch Gen Psychiatry*. 1978;35:837-844.
27. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Third Edition*. Washington, DC: American Psychiatric Association; 1980.
28. Colombotos J. Personal vs. telephone interviews. *Public Health Rep*. 1969;84: 773-782.
29. Weeks M, Kulka R, Lessler J, Whitmore R. Personal versus telephone surveys for collecting household data at the local level. *Am J Public Health*. 1983;73: 1389-1394.
30. Aneshensel C, Frerichs R, Clark V, Yokopanic P. Telephone vs. in-person surveys of community health surveys. *Am J Public Health*. 1982;72:1017-1021.
31. Rhode P, Lewinsohn P, Seeley R. Comparability of telephone and face-to-face interviews in assessing axis I and II disorders. *Am J Psychiatry*. 1997;154: 1593-1598.
32. Andreasen NC, Endicott J, Spitzer RL, Winokur G. The family history method using diagnostic criteria. *Arch Gen Psychiatry*. 1977;34:1229-1235.
33. Hedeker D. *MIXNO: A Computer Program for Mixed-Effects Nominal Logistic Regression*. Chicago: University of Illinois at Chicago, School of Public Health and Prevention Research Center; 1998. Technical Report.
34. Regier D, Farmer M, Rae D, Locke BZ, Keith SJ, Judd LL, Goodwin FK. Comorbidity of mental disorders with alcohol and other drug abuse: results from the Epidemiologic Catchment Area (ECA) Study. *JAMA*. 1990;264:2511-2518.
35. Warner L, Kessler R, Hughes M, Anthony J, Nelson C. Prevalence and correlates of drug use and dependence in the United States. *Arch Gen Psychiatry*. 1995; 52:219-229.
36. Cloninger CR, Christiansen KO, Reich T, Gottesman II. Implications of sex differences in the prevalence of antisocial personality, alcoholism, and criminality for familial transmission. *Arch Gen Psychiatry*. 1978;35:941-951.
37. Hill SY, Smith TR. Evidence for genetic mediation of alcoholism in women. *J Subst Abuse*. 1991;3:159-174.
38. Merikangas K, Brunetto W. Assortative mating and psychiatric disorders. In: Papadimitriou G, Mendlewicz J, eds. *Bailliere's Clinical Psychiatry: International Practice and Research*. London, England: Bailliere Tindall; 1996:175-185.
39. Annis H. Patterns of intra-familial drug use. *Br J Addict*. 1974;69:361-369.
40. Bauman KE, Foshee VA, Linzer MA, Koch GG. Effect of parental smoking classification on the association between parental and adolescent smoking. *Addict Behav*. 1990;15:413-422.
41. Duncan TE, Duncan SC, Hops H, Stoolmiller M. An analysis of the relationship between parent and adolescent marijuana use via generalized estimating equation methodology. *Multivariate Behav Res*. 1995;30:317-339.
42. Khantzian EJ. The self-medication hypothesis of addictive disorders: focus on alcohol and cocaine dependence. *Am J Psychiatry*. 1985;142:1259-1264.
43. Weiss R, Griffin M, Mirin S. Drug abuse as self-medication for depression: an empirical study. *Am J Drug Alcohol Abuse*. 1992;18:121-129.
44. Barnes G, Welte J. Patterns and predictors of alcohol use among 1-12th grade students in New York State. *J Stud Alcohol*. 1986;47:53-62.
45. Brook JS, Whiteman M, Gordon AS, Cohen P. Some model mechanisms for explaining the impact of maternal and adolescent characteristics on adolescent stage of drug use. *Dev Psychol*. 1986;22:460-467.
46. Bailey SL, Hubbard RL. Developmental variation in the context of marijuana initiation among adolescents. *J Health Soc Behav*. 1990;31:58-70.
47. Robins LN. The natural history of drug abuse. *Acta Psychiatr Scand Suppl*. 1980; 284:7-20.
48. Farrington DP. Longitudinal research strategies: advantages, problems and prospects. *J Am Acad Child Adolesc Psychiatry*. 1991;30:369-374.
49. Brown SA. Life events of adolescents in relation to personal and parental substance abuse. *Am J Psychiatry*. 1989;146:484-489.
50. Holden MG, Brown SA, Mott MA. Social support network of adolescents: relation to family alcohol abuse. *Am J Drug Alcohol Abuse*. 1988;14:487-498.
51. Roosa MW, Beals J, Sandler IN, Pillow DR. The role of risk and protective factors in predicting symptomatology in adolescent self-identified children of alcoholic parents. *Am J Community Psychol*. 1990;18:725-741.
52. McCarthy WJ, Anglin MD. Narcotics addicts. *J Drug Issues*. 1990;20:99-123.
53. Brook JS, Brook DW, Gordon AS, Whiteman M, Cohen P. The psychosocial etiology of adolescent drug use. *Genet Soc Gen Psychol Monogr*. 1990;116:111-267.
54. Kandel DB, Andrews K. Processes of adolescent socialization by parents and peers. *Int J Addict*. 1987;22:319-342.
55. Kumpfer KL, Hopkins R. Recent advances in addictive disorders: prevention: current research and trends. *Psychiatr Clin North Am*. 1993;16:11-20.
56. Simcha-Fagan O, Schwartz J. Neighborhood and delinquency: an assessment of contextual effects. *Criminology*. 1986;24:667-703.