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# Common genetic mechanisms in alcohol, drug, and mental disorder comorbidity

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**Abstract**

Comorbid drug and mental disorders were assessed in 63 monozygotic (MZ) and 67 dizygotic (DZ) twin pairs. DSM-III alcohol dependence was heritable in males when probands had a comorbid DSM-III drug or mental disorder but not when probands had only alcohol dependence. For males, significantly higher cross-MZ than cross-DZ correlations were found between alcohol dependence in probands and certain mental and drug disorders in cotwins. In contrast, females showed higher within-twin than cross-MZ correlations and similar cross-MZ and cross-DZ correlations between alcohol dependence and all mental and drug disorders. These results suggest comorbidity between alcohol and certain drug and mental disorders in males in epidemiological surveys may be due in part to genetic influences.

*Keywords:* Genetics; Comorbidity; Twins; Alcoholism; Drug abuse; Mental disorders

## 1. Introduction

Comorbidity among alcohol, drug, and mental disorders is well recognized. Individuals with one disorder have higher rates of the other disorders than individuals in the general population (Crowley et al., 1974; Rounsaville et al., 1982; Helzer and Pryzbek, 1988; Ross et al., 1988). In a community-based study, alcoholics were 7.1 times more likely to have a drug disorder and 2.3 times more likely to have a mental disorder than individuals in the remainder of the population (Regier et al., 1990). For younger adults, having a depressive or anxiety disorder doubled the risk for subsequent development of a drug disorder (Christie et al., 1988).

Alcohol, drug, and mental disorders also co-occur at higher than expected rates in relatives of affected individuals. Relatives of alcoholic probands have higher rates of depression and drug abuse than controls (Winokur et al., 1970; Gershon et al., 1975; Hill et al., 1977; Cloninger et al., 1979; Schuckit, 1979; Winokur, 1979; Johnson et al., 1989), and elevated rates of alcoholism, depression, and antisocial personality occur in relatives of opiate-abusing probands compared to controls (Rounsaville et al., 1991; Luthar et al., 1992). The familial aggregation of alcohol, drug, and mental disorders suggests a common etiology, which may be due to genetic and/or environmental factors.

Common or closely-linked genes may produce a general susceptibility to all three disorders, with manifestation of specific disorders being due to other genetic and/or environmental factors. Certain mental disorders (generalized anxiety disorder, antisocial personality disorder) share diagnostic symptoms with substance use disorders (American Psychiatric Association, 1980), consistent with a hypothesis of pleiotropy or genetic linkage. At one time, alcoholism and depression were suggested to result from a common underlying disorder that manifested itself primarily as alcoholism in males

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and depression in females (Winokur et al., 1971). However, family study data have generally not supported this theory (Cloninger et al., 1978; Merikangas et al., 1985).

Comorbidity among alcohol, drug, and mental disorders may also result from common environmental influences, or from one disorder serving as an influence that predisposes to the other disorders. The association between depression or anxiety and alcohol (Schuckit, 1986) and other drug (Woody et al., 1975) use has been recognized clinically. In experimental studies, alcohol preload increases other drug self-administration (Henningfield et al., 1984), and depression and/or anxiety are increased during experimental re-addiction to opiates (Haertzen and Hooks, 1969; Mirin et al., 1976) or alcohol (Mendelson et al., 1968).

Recently, common influences in comorbidity between alcoholism and major depression were examined in a population-based twin study of women (Kendler et al., 1993). Co-occurrence of alcoholism and major depression in women was found to be due largely to genetic influences, although common environmental influences were also implicated. The present twin study extended this analysis by exploring genetic influences on comorbidity between alcoholism and a number of mental and drug disorders. Males as well as females were employed as subjects. Probands were ascertained from treatment programs where comorbidities between alcoholism and other disorders are over-represented (Kessler et al., 1994).

The purpose of the study was twofold. First, the effect of having a comorbid drug or mental disorder was examined on concordance for alcohol dependence in monozygotic (MZ) and dizygotic (DZ) twins to determine if the observed comorbidity was attributable to common genetic factors. Clinical characteristics of probands with and without comorbid drug or mental disorder were compared. Second, within-twin and cross-twin correlations between alcohol dependence and specific drug or mental disorders were compared to determine which mental and drug disorders are genetically correlated with alcoholism. Common genetic influences in comorbidity would be suggested by higher cross-MZ than cross-DZ twin correlations between alcoholism and another disorder. On the other hand, lack of common genetic influences would be suggested by higher within-twin than cross-MZ twin correlations, and by similar cross-MZ and cross-DZ twin correlations. Specifically, higher within-twin than cross-MZ twin correlations indicate the presence of environmental influences unique to the individual (i.e., not shared within the twin pair or within the family) that increase susceptibility to both alcoholism and another disorder, whereas similar cross-MZ and cross-DZ twin correlations indicate environmental influences that are experienced by both members of a twin pair as increasing susceptibility to alcoholism and another disorder.

## 2. Methods

Data in the present study were collected as part of a twin study of alcoholism previously reported (Pickens et al., 1991). Briefly, a total of 599 twins were identified by screening records from alcohol and drug abuse treatment programs. Both members of 392 twin pairs were located and agreed to participate. Each pair member was initially administered a written questionnaire that included items on demography, pair similarity, and personal and family alcohol and drug use. A subsample of these individuals was later directly interviewed using the Diagnostic Interview Schedule (DIS) (Version III-A) (Robins et al., 1981) and other assessment scales. Zygosity was determined either by analysis of 12 serological factors (94% of cases) or on the basis of questionnaire responses concerning pair similarity as children (6% of cases).

### *2.1. Subject characteristics*

The present report is based on data from 130 same-sex pairs (probandwise count) from the original sample in which the proband met DSM-III criteria for alcohol dependence (American Psychiatric Association, 1980), both members of each twin pair were personally interviewed, and zygosity was determinable. Subjects meeting criteria for DSM-III alcohol abuse only were not included, as no evidence was found earlier of genetic involvement in this subtype of alcoholism (Pickens et al., 1991). Included in the sample were 39 MZ and 47 DZ males and 24 MZ and 20 DZ females. For both males and females, MZ and DZ probands did not differ in race, education, or marital status. However, MZ male probands were approximately 6 years younger than DZ male probands ($P = 0.02$) at the time of the interview. There was no significant difference in age at interview of MZ and DZ female probands. Similarly, except for MZ male probands having an earlier age of onset of alcohol problems than DZ male probands ($P = 0.04$) and DZ male probands more frequently reporting the use of a quart or more of alcohol per drinking occasion ($P = 0.05$), no other MZ/DZ differences for either male or female probands were found on a variety of alcohol-related measures including frequency of alcohol use, number of alcoholism symptoms, or percent having sought previous alcoholism treatment.

A subsample of admissions to a participating treatment program screened between February, 1985 and June, 1986 yielded a twinning rate of 1.6%, which is similar to the population twinning rate of 2.4% (Fuller and Thompson, 1978). Zygosity rates for these twins (based on response to questionnaire items) were 48% MZ and 52% same-sex DZ, which are also within general population rates of 46–51% MZ and 49–54% same-sex DZ (Gottesman and Shields, 1982). Finally, except for being somewhat younger, the alcoholic twins did not

differ from other clients in the treatment programs in terms of sex ratio, marital status, education level, or type of substances used (Svikis and Pickens, 1991).

### 2.2. Clinical diagnoses

Diagnoses of lifetime alcohol, drug, and mental disorders were based on DSM-III criteria applied to DIS responses using standard algorithms (American Psychiatric Association, 1980). All probands met criteria for lifetime alcohol dependence. Drug disorder was defined by abuse and/or dependence on barbiturates, opiates, cocaine, amphetamines, cannabis, or hallucinogens. Diagnosis of antisocial personality disorder followed standard diagnostic procedures except alcohol-related symptoms were not used. Diagnostic rates and rates of co-occurrence of drug and/or mental disorder are presented in Table 1. Because certain mental disorders occurred too infrequently for meaningful statistical analysis, only those with a lifetime prevalence of $\geq 10\%$ in probands were included. Mental disorders excluded were mania (2%), schizophrenia (2%), anorexia (0%), bulimia (3%), organic brain disorder (9%), somatization disorder (0%), and compulsive gambling (4%).

### 2.3. Data analysis

Twins were concordant if both proband and cotwin were affected with the same disorder, and cross-concordant if the proband was affected with one disorder and the cotwin was affected with a second disorder. In the present study, concordance and cross-concordance rates were transformed into tetrachoric correlations using population base rates (adjusted for the characteristics of the sample) obtained from the National Institute of Mental Health Epidemiological Catchment Area (ECA) Survey Public Use Data Set, Wave 1 Household Sample (Eaton and Kessler, 1985). Base rates were determined by analysis of the public domain data-tape for the two sites (St. Louis, MO and Los Angeles, CA) that administered the DIS alcohol section using the same skipout procedures as in the present study. The diagnostic rates for whites (93% of sample) were computed in 5-year age intervals, separately for males and females, in the two sites combined. The tetrachoric correlations provide evidence consistent with genetic factors underlying comorbidity if the cross-MZ correlation significantly exceeds the cross-DZ correlation. Intra-individual environmental factors are significant in the co-occurrence of two disorders if the two traits are more highly correlated within an individual than across members of MZ twin pairs.

Cross-concordance rates for alcoholism in the proband and drug or mental disorder in the cotwin were calculated using the probandwise method (Allen et al., 1967; McGue, 1992). MZ and DZ concordance rates were compared with Pearson $\chi^2$ statistic using one-tailed probability values to test the hypothesis of greater MZ than DZ concordance. Tetrachoric correlations (and standard errors) and bivariate heritability were calculated following the methods outlined by Digby (1983) and Plomin and DeFries (1979), respectively. All demographic and other group comparisons were by Pearson $\chi^2$ and Student $t$ statistics using two-tailed probability values. Fisher's exact test was used when any expected cell value in a $2 \times 2$ contingency table was less than 5.

## 3. Results

Approximately half of MZ and DZ probands met DSM-III criteria for any drug disorder (abuse and/or dependence) and significant proportions of the MZ and DZ probands also met DSM-III criteria for various mental disorders (Table 1). Except for obsessive compulsive disorder in females, there was no significant difference between MZ and DZ probands in prevalence of any drug disorder or any mental illness for either male or female subjects ($P > 0.05$).

### 3.1. Alcoholism concordance

The presence of mental disorders in the proband significantly influenced pair concordance for alcoholism in males (Table 2). Male alcoholic MZ probands with any type of mental illness were more likely ($P = 0.03$) to have a cotwin who was alcoholic than male alcoholic MZ probands without a mental disorder. The same was not true for male DZ twins with and without a mental disorder. More importantly, MZ/DZ differences in pair concordance for alcohol dependence were significant ($P = 0.003$) only if a mental disorder was present in the proband (MZ/DZ ratio = 2.0 for mental disorder present, 0.85 for mental disorder absent). The influence of proband mental disorder on concordance for alcoholism in females could not be determined due to the small number of alcoholic female probands with no mental disorder ($n$ = 3 MZ, 4 DZ). However, significant differences in MZ/DZ concordance for alcohol dependence were found for female probands with a mental illness (MZ = 0.26, DZ = 0.00, $P = 0.02$, data not shown).

Likewise, having a drug disorder in the alcoholic proband contributed to MZ/DZ differences in concordance for alcoholism in males (Table 2). A significant difference in MZ/DZ concordance for alcohol dependence was found in pairs where the proband had a comorbid drug disorder (MZ/DZ ratio = 2.5 for drug disorder present, 1.3 for drug disorder absent). In females, although MZ concordance was somewhat higher than DZ concordance both for probands with and without a comorbid drug disorder, the MZ/DZ difference was not statistically significant.

In general, probands (both male and female, MZ and DZ) with a comorbid drug disorder were younger in age at interview, at first alcohol intoxication, and at first

Table 1
Diagnostic rates (%) and rates of co-occurrence (%) of drug and/or mental disorders in probands

| | Male probands | | Female probands | |
|---|---|---|---|---|
| | MZ ($n$ = 39) | DZ ($n$ = 47) | MZ ($n$ = 24) | DZ ($n$ = 20) |
| Mental disorders | | | | |
| Major depression | 20.5 | 21.3 | 45.8 | 60.0 |
| Dysthymia | 10.3 | 14.9 | 29.2 | 20.0 |
| Antisocial personality | 35.9 | 40.4 | 37.5 | 30.0 |
| Generalized anxiety | 41.0 | 44.7 | 62.5 | 70.0 |
| Obsessive-compulsive | 17.9 | 12.8 | 12.5 | 40.0 |
| Phobia | 33.3 | 36.2 | 33.3 | 55.0 |
| Panic attack | 2.6 | 8.5 | 8.3 | 25.0 |
| Drug disorders | | | | |
| Barbiturates | 15.4 | 21.3 | 25.0 | 20.0 |
| Opiates | 12.8 | 8.5 | 16.7 | 10.0 |
| Cocaine | 12.8 | 8.5 | 16.7 | 10.0 |
| Amphetamines | 28.2 | 27.7 | 12.5 | 20.0 |
| Cannabis | 41.0 | 29.8 | 41.7 | 25.0 |
| Hallucinogens | 7.7 | 0.0 | 0.0 | 0.0 |
| Any drug disorder | 53.8 | 42.6 | 58.3 | 45.0 |
| Rates of co-occurrence | | | | |
| Alcohol only | 25.6 | 23.4 | 8.3 | 15.0 |
| Alcohol and drug only[a] | 7.7 | 8.5 | 4.2 | 0.0 |
| Alcohol and mental only | 20.5 | 34.0 | 33.3 | 40.0 |
| Alcohol, drug[a] and mental | 46.2 | 34.0 | 54.2 | 45.0 |

[a]Excluding tobacco and alcohol.

alcohol problem, and had a greater number of alcohol symptoms than probands without a drug disorder. The probands did not differ, however, in race, education, marital status, or quantity or frequency of alcohol use. In contrast, male probands with and without a comorbid mental disorder were not significantly different on any of these same demographic or clinical characteristics. Clinical characteristics of female probands with and without a comorbid mental disorder were not compared due to the small number of female probands without comorbid mental disorder.

### 3.2. Cross-concordance

Cotwin risk for mental or drug disorder was determined in all twin pairs, separate by sex, without regard to additional diagnoses in either the proband or cotwin. Within- and cross-twin correlations between alcohol dependence and specific mental and drug disorders are presented in Table 3. In some cases, tetrachoric correlations couid not be computed due to low cell frequencies. For both males and females, within-twin correlations were similar across all drug and mental disorders, and all within-twin correlations were significantly greater than zero ($P < 0.01$).. For males, within-twin correla-

Table 2
Concordance for alcoholism as a function of comorbid mental[a] or drug[b] disorder in the proband (concordance rate/number)

| | Mental disorder in proband | | | Drug disorder in proband | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Male subjects | | | Male subjects | | | Female subjects | | |
| | Present | Absent | $P$ | Present | Absent | $P$ | Present | Absent | $P$ |
| MZ | 0.70 (19/27) | 0.33 (4/12) | 0.03 | 0.62 (13/21) | 0.56 (10/18) | ns | 0.29 (4/14) | 0.20 (2/10) | ns |
| DZ | 0.35 (12/34) | 0.39 (5/13) | ns | 0.25 (5/20) | 0.44 (12/27) | ns | 0.00 (0/9) | 0.09 (1/11) | ns |
| $P$ | 0.003 | ns | | 0.01 | ns | | ns | ns | |

[a]Concordance rates for females are not presented due to the small number of female probands without any mental illness ($n$ = 3 MZ, 4 DZ).
[b]Defined as drug abuse and/or drug dependence.

Table 3
Tetrachoric correlations between alcohol dependence and mental and drug disorders

| Comorbid alcohol dependence and: | Males | | | | Females | | | |
|---|---|---|---|---|---|---|---|---|
| | Within-twin | Cross-MZ | Cross-DZ | MZ/DZ *P* | Within-twin | Cross-MZ | Cross-DZ | MZ/DZ *P* |
| Major depression | 0.51 | 0.54 | 0.32 | 0.13 | 0.53 | 0.18 | 0.20 | 0.50 |
| Dysthymia | 0.47 | 0.28 | 0.01 | 0.28 | 0.42 | 0.31 | [a] | [a] |
| Antisocial personality | 0.55 | 0.63 | 0.47 | 0.05 | 0.60 | 0.22 | 0.21 | 0.49 |
| Obsessive-compulsive | 0.60 | 0.37 | 0.27 | 0.39 | 0.52 | 0.22 | [a] | [a] |
| Phobia | 0.61 | 0.47 | 0.13 | 0.06 | 0.41 | 0.26 | 0.31 | 0.50 |
| Panic | 0.47 | 0.52 | 0.25 | 0.26 | 0.41 | 0.09 | 0.09 | 0.50 |
| Barbiturates | 0.67 | 0.37 | [a] | [a] | 0.64 | 0.23 | 0.21 | 0.49 |
| Opiates | 0.58 | 0.14 | [a] | [a] | 0.68 | 0.41 | 0.46 | 0.50 |
| Cocaine | 0.78 | [a] | [a] | [a] | 0.76 | 0.48 | [a] | [a] |
| Amphetamines | 0.72 | 0.68 | 0.05 | 0.03 | 0.44 | 0.28 | [a] | [a] |
| Cannabis | 0.59 | 0.56 | 0.26 | 0.04 | 0.61 | 0.38 | [a] | [a] |
| Hallucinogens | 0.58 | [a] | [a] | [a] | [a] | [a] | [a] | [a] |

[a]Not able to estimate due to low cell frequency.

tions were not significantly higher than cross-MZ twin correlations for any drug or mental disorder ($P > 0.05$ in all cases). When cross-correlations between alcohol dependence in proband and another disorder in cotwin were compared in males, the cross-MZ correlation was significantly higher than the cross-DZ correlation for antisocial personality ($P = 0.05$), amphetamine abuse/dependence ($P = 0.03$) and cannabis abuse/dependence ($P = 0.04$), and marginally significant for phobia ($P = 0.06$). For females, significantly higher within- than cross-MZ twin correlations were found between alcohol dependence in proband and major depression ($P = 0.02$) and antisocial personality ($P = 0.02$) in cotwin. No significant difference between cross-MZ and cross-DZ twin correlations was found in females for any drug or mental disorder.

## 4. Discussion

These results suggest that co-occurrence of certain mental and drug disorders often observed in alcoholics and their families may have a common genetic basis, at least for males. In females, the co-occurrence of alcohol dependence and other mental disorders and alcohol and drug disorders may be more likely due to environmental factors, although a small sample size and low base rates of certain disorders in females require caution in interpretation of these results. Since a number of disorders in males were found to have a common genetic influence, it may be more useful to study these disorders in combination in future studies than to examine them separately.

### *4.1. Heritability of alcoholism*

Alcoholism in males appears to be more heritable when the proband has either a comorbid drug or mental disorder. Higher MZ than DZ concordance for alcohol dependence was found only when probands had a comorbid drug or mental disorder. No difference in MZ and DZ concordance for alcohol dependence was seen in probands without comorbid drug or mental disorders. This suggests the genetic aspects of alcoholism in males are inherently associated with comorbidity for mental and drug disorders, at least in a treatment-seeking population. However, the nature of this association is not clear. From a genetic perspective, alcohol, drug, and mental disorders could in part reflect alternative manifestations of a common genetic condition. Alternatively, alcoholism could be a final common pathway for a number of genetically determined conditions. Environmental factors could also influence the expression of this genetic condition, or be responsible for similar-appearing phenotypes of the same disorders.

Alcoholic probands with comorbid drug disorder were younger and reported earlier ages of first alcohol intoxication and alcohol problems than probands without a comorbid drug disorder. This suggests age of onset may be an indication of genetic influences in alcoholism but only when alcoholism co-occurs with drug disorders. Cloninger et al. (1981) have suggested early age of onset of alcohol problems is associated with greater genetic influence in alcoholism in men. In a recent twin study, however, cotwin risk for alcohol dependence was related to zygosity but not to proband age of onset of alcohol problems (Pickens et al., 1991). In the present study, genetic influences in alcoholism were only evident in males with comorbid drug or mental disorders. However, since our alcoholic probands with drug disorders were younger than the probands without drug disorders, this association between age of onset

and genetic influences in alcoholism may be only a cohort effect (Kessler et al., 1994).

*4.2. Common genetic etiology*

In the present study, cross-concordances were transformed into cross-correlations to quantify genetic contribution to covariance between disorders. This was done to control for mechanisms of transmission other than genetic that might be responsible for MZ and DZ differences in cross-concordance rates (Kendler et al., 1992). For example, MZ/DZ differences in cross-concordance for alcoholism and a given mental disorder might be due to genetic influences on alcoholism only, with the mental disorder being environmentally related to alcoholism.

An alternative to using correlational comparisons as a method for controlling for environmental influences is to eliminate cases where comorbidity was also present in the proband or alcoholism was also present in the cotwin. While this approach may be intuitively appealing, it is highly conservative and undoubtedly results in an underestimate of genetic overlap between alcohol and mental and drug disorders. Not only does it result in a significant reduction in statistical power, but by removing cases of comorbidity in the proband and cotwin it may be eliminating the most significant cases from a genetic perspective. By allowing such cases to remain, the correlational approach used here is most appropriate for these types of analyses.

For males, the cross-MZ correlations between alcohol dependence and antisocial personality, phobia, and amphetamine and cannabis abuse/dependence were not significantly different from the within-twin correlations, while the cross-MZ correlations were significantly larger than the cross-DZ correlations. This suggests genetic factors are involved in the comorbidity between these disorders and alcoholism in males. For females, the correlational pattern was considerably different, with higher within-twin than cross-MZ correlations and equal cross-MZ and cross-DZ correlations in general. Evidence for significant intra-individual environmental but not genetic factors were found in the co-occurence between alcohol dependence and major depression and alcohol dependence and antisocial personality.

Although no significant cross-MZ/cross-DZ difference was found between alcohol dependence and major depression ($P = 0.13$) and panic disorder ($P = 0.26$) in males, the pattern of within-twin and cross-twin correlations is nevertheless suggestive of a genetic influence. In both cases, similar within-twin and cross-MZ twin, and higher cross-MZ than cross-DZ correlations, were found.

The relationship between substance use and mental disorders has been examined in a number of family studies (Cloninger, 1987a; George et al., 1990; Kosten et al., 1991; Luthar et al., 1992; Mirin et al., 1991; Rounsaville et al., 1991). Reich et al. (1981) examined the prevalence of alcoholism and antisocial personality in relatives of probands with alcoholism and/or antisocial personality. Higher rates of alcoholism were found in relatives of probands having alcoholism only, and higher rates of antisocial personality were found in relatives of probands having antisocial personality only, than occurred across disorders. However, higher rates of alcoholism or antisocial personality were found in relatives of probands having both disorders than in relatives of probands having alcoholism only or antisocial personality only. While these findings were interpreted by the authors as suggesting independent transmission of the two disorders (Reich et al., 1981), the results of the present study suggest they might also reflect greater genetic involvement in alcoholism for alcoholics with antisocial personality than in alcoholics without antisocial personality. Alcoholism is also more prevalent among first-degree relatives of probands with phobia or panic disorder than controls. In another study, rates of alcoholism were 31% in male relatives of individuals with agoraphobia, 14% in male relatives of individuals with panic disorder, and 10% in male relatives of controls (Noyes et al., 1986).

Similarly, the association between illicit drug and alcohol disorders has also received significant research attention. Several studies have reported that transmission of drug and alcohol disorders is independent (Croughan, 1985; Mirin et al., 1991) with one study reporting the specificity of transmission differs by sex (Mirin et al., 1991). Studies of the specificity of transmission of drug and alcohol abuse have focused almost exclusively on parent-offspring resemblance. Secular trends in the availability and patterns of use of addictive drugs, however, limit the conclusions that can be drawn from parent-offspring comparisons. At least one family study of substance abuse has focussed on studying siblings in order to control for such factors (Luthar et al., 1992).

Biological relatives of alcoholics also appear to be at increased risk for depression (Gershon et al., 1975; Cloninger et al., 1979; Schuckit, 1979; Winokur, 1979), consistent with a theory of a common etiology for the two disorders. However, when relatives of depressed probands are considered, some studies find elevated risk for alcoholism in family members of depressed probands (Winokur, 1982; Winokur et al., 1982) whereas others do not (Gershon et al., 1982; Weissman et al., 1984). In one family study, relatives of depressed probands were found to be at increased risk for alcoholism if the proband was also alcoholic but were not at increased risk for alcoholism if the proband was depressed but not alcoholic (Merikangas et al., 1985). In contrast, Winokur and Coryell (1991) found elevated rates of alcoholism in family members of probands who were depressed but not alcoholic, but only in the relatives of female probands.

While it would be tempting to speculate about a single

neurochemical mechanism that mediates the common genetic influence seen here, it is clearly premature to do so. For example, the serotonergic system has been implicated in antisocial behavior (Lewis, 1991), depression (Leonard, 1994) and anxiety (Klerman, 1992) states, and alcohol (Sellers et al., 1992) and cocaine (Sellers et al., 1991) abuse. However, dopaminergic and noradrenergic systems have also been implicated in these same disorders (Cloninger, 1987a; Cloninger, 1987b), and other disorders with serotonergic involvement (i.e., obsessive compulsive disorder) were not found to have genetic mechanisms in common with alcoholism. Thus, as they are currently conceptualized, clinical disorders lack the neurochemical specificity that is necessary to link them to a common genetic effect. Reducing the clinical disorders to more basic psychopathological dimensions (e.g., impulsiveness, aggression) may offer greater hope for understanding their common genetic features (Van Praag et al., 1990).

The results also demonstrate the importance of environmental factors in comorbidity between alcoholism and drug disorders. Within-twin correlations between alcohol dependence and a number of mental and drug disorders were higher than cross-MZ twin correlations indicating the importance of environmental factors specific to the individual. Similar cross-MZ and cross-DZ correlations between these disorders and alcoholism were also obtained indicating a role for familial environmental factors. While this was especially true for women, a smaller sample size reduces confidence in these findings. The mere presence of common genetic influences between disorders does not rule out environmental influences. Nor does failure to show genetic effects demonstrate environmental influences. Depression and anxiety increase in alcoholics during experimental alcohol administration (Mendelson et al., 1968) and often clears after treatment (Schuckit, 1986). In addition, experimental alcohol admininstration is associated with increased rates of other drug self-administration (Griffiths et al., 1976).

### 4.3. Sex differences

In the present study, considerable comorbidity among alcohol, drug, and mental disorders was found for both male and female probands. Cotwins of male and female alcoholic probands were also at significant risk for drug and mental disorders. Cross-MZ/cross-DZ comparisons indicated a common genetic influence between alcohol dependence and certain mental and drug disorders in males only. No evidence was found suggesting a common genetic influence between these disorders in females.

Our failure to find common genetic effects on alcoholism and other mental and drug disorders in women is consistent with the recent finding from a multivariate genetic analysis of data on more than 1000 pairs of female twins that the genetic factors influencing alcoholism are largely distinct from the genetic factors that influence phobia, generalized anxiety disorder, panic disorder, bulimia, and major depression (Kendler et al., 1995). Our finding of common genetic influences in alcoholism and other mental and drug disorders in men provide additional support for the proposition that there are distinct aspects to the inheritance of alcoholism in men and women (McGue and Slutske, 1993).

Previous adoption and twin studies suggest there may be differences between males and females in etiology of alcohol disorder or with regard to underlying etiology of comorbid disorders (Goodwin et al., 1977; Gurling et al., 1981; McGue et al., 1992). Such differences are difficult to assess, however, due to the relatively small number of women that have been studied (McGue and Slutske, 1993; Svikis and Pickens, 1994). It is important, therefore, that future family, twin, and adoption studies of alcoholism focus on both women and men.

### 4.4. Limitations

There are several limitations to the study. First, alcoholic twins may not be representative of alcoholic non-twins. However, since the number of twins in treatment was comparable to what would be expected from population twinning estimates, the risk for alcoholism did not appear to be different for twins and non-twins. Although no differences were found between twins and non-twins from the same alcoholism treatment program on a number of demographic measures, a more detailed comparison of twins and non-twins is needed to address this issue.

Second, the twin study method is based on certain assumptions that may not be valid. Among these is the equal environments assumption, which holds that MZ and DZ twins have equally similar intrapair environments. Within the present study, degree of within-pair closeness (i.e., frequency, amount, type, and quality of contact) was found to differ significantly in MZ and DZ twin pairs. However, degree of closeness was unrelated to concordance for alcohol abuse/dependence (LaBuda and Pickens, 1995). While degree of closeness was related to concordance for drug abuse/dependence, MZ/DZ difference in concordance for drug abuse/dependence remained significant when zygosity differences in closeness were statistically controlled.

A third limitation is that, although the correlational analyses were conducted as if the data were drawn from a population study, they were not. Instead, population base rates for drug and mental disorders were obtained from data provided by the ECA study (Eaton and Kessler, 1985), adjusted to characteristics of the present subject sample. Although only data from ECA sites administering the DIS in the same manner as the present study were employed, that data may not be representative of the present subject sample.

A fourth factor that limits conclusions from the present study is the size of the twin sample. The sample in-

cluded a total of 86 male and 44 female twin pairs. Although samples of this size are comparable to those found in most other published twin studies of alcoholism (McGue, 1994), the size of our sample requires that our conclusions be tentative (especially in the female sample) and precludes our use of more powerful multivariate genetic methods than those used here (Kendler et al., 1995).

Finally, subjects were ascertained through alcohol treatment programs rather than the general population. Previously, the strongest evidence for genetic influences in female alcoholism has come from a twin population-based study (Kendler et al., 1993). As a group, adoption studies have found only slightly higher rates of alcohol abuse in adopted-away daughters of alcoholics (4.7%) compared to adopted-away daughters of non-alcoholics (3.1%) (McGue, 1994). Treatment-based studies employing females as subjects have either failed to find evidence of genetic influences in alcoholism (Roe, 1944; Goodwin et al., 1977; McGue et al., 1992) or found lower heritabilities than reported in the population-based study (Kendler et al., 1993). Thus, different results may be obtained with treatment-based and population-based samples. Although alcoholic individuals in treatment have higher than expected rates of comorbid mental and drug disorders (Helzer and Pryzbek, 1988; Kessler et al., 1994), there is no evidence that individuals with comorbidities in treatment populations are not representative of individuals with comorbidities in the general population.

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## References

Allen, G., Harvald, B. and Shields, J. (1967) Measures of twin concordance. Acta Genet. Med. Gemellol. 17, 475–481.

American Psychiatric Association (1980) Diagnostic and Statistical Manual of Mental Disorders, Third Edition, American Psychiatric Association, Washington, DC.

Christie, K.A., Burke, J.D., Regier, D.A., Rae, D.S., Boyd, J.H. and Locke, B.Z. (1988) Epidemiological evidence for early onset of mental disorders and higher risk of drug abuse in young adults. Am. J. Psychiatry 145, 971–975.

Cloninger, C.R. (1987a) Neurogenetic adaptive mechanisms in alcoholism. Science 236, 410–416.

Cloninger, C.R. (1987b) Recent advances in the genetics of anxiety and somatoform disorders. In: Psychopharmacology: The Third Generation of Progress (Meltzer, H.Y., ed.), pp. 955–965. Raven Press, New York.

Cloninger, C.R., Bohman, M. and Sigvardsson, S. (1981) Inheritance of alcohol abuse: cross fostering analysis of adopted men. Arch. Gen. Psychiatry 38, 861–868.

Cloninger, C.R., Christiansen, K.O., Reich, T. and Gottesman, I.I. (1978) Implications of sex differences in the prevalences of antisocial personality, alcoholism, and criminality for familial transmission. Arch. Gen. Psychiatry 35, 941–951.

Cloninger, C.R., Reich, T. and Wetzel, R. (1979) Alcoholism and affective disorders: familial associations and genetic models. In: Alcoholism and Affective Disorders: Clinical, Genetic and Biochemical Studies (Goodwin, D.W. and Erikson, C.K., eds.), pp. 57–86. SP Medical and Scientific Books, New York.

Croughan, J.L. (1985) The contribution of family studies to understanding drug abuse. In: Studying Drug Abuse, Series in Psychosomatic Epidemiology (Robins, L.N., ed.), pp. 93–116. Rutgers University Press, New Brunswick, NJ.

Crowley, T.J., Chesluk, D., Dilts, S. and Hart, R. (1974) Drug and alcohol abuse among psychiatric admissions. Arch. Gen. Psychiatry 30, 13–20.

Digby, P.G.N. (1983) Approximating the tetrachoric correlation coefficient. Biometrics 39, 753–757.

Eaton, W.W. and Kessler, R.C. (1985) Epidemiology Field Methods in Psychiatry: The NIMH Epidemiological Catchment Area Program, Academic Press, Orlando.

Fuller, J.L. and Thompson, W.R. (1978) Foundations of Behavior Genetics, CV Mosby, St. Louis.

George, D.T., Nutt, D.J., Dwyer, B.A. and Linnoila, M. (1990) Alcoholism and panic disorder: is the comorbidity more than coincidence? Acta Psychiatr. Scand. 81, 97–107.

Gershon, E.S., Hamovit, J., Guroff, J.J., Dibble, E., Leckman, J.F., Sceery, W., Targum, S.D., Nurnberger, J.I., Goldin, L.R. and Bunney, W.E. (1982) A family study of schizoaffective, bipolar I, bipolar II, unipolar, and normal control probands. Arch. Gen. Psychiatry 39, 1157–1167.

Gershon, E.S., Mark, A., Cohen, N., Belizon, N., Baron, M. and Knobe, K. (1975) Transmitted factors in the morbid risk of affective disorders: a controlled study. J. Psychiatr. Res. 12, 283–289.

Goodwin, D.W., Schulsinger, F., Knop, J., Mednick, S. and Guze, S.B. (1977) Alcoholism and depression in adopted and non-adopted daughters of alcoholics. Arch. Gen. Psychiatry 34, 751–755.

Gottesman, I.I. and Shields, J. (1982) Schizophrenia: The Epigenetic Puzzle, Cambridge University Press, Cambridge, MA.

Griffiths, R.R., Bigelow, G.E. and Liebson, I. (1976) Facilitation of human tobacco self-administration by ethanol: a behavioral analysis. J. Exp. Anal. Behav. 25, 279–292.

Gurling, H.M.D., Murray, R.M. and Clifford, C.A. (1981) Investigations into the genetics of alcohol dependence and into its effects on brain function. In: Twin Research 3: Epidemiology and Clinical Studies (Nance, W.E., Parisi, P. and Gedda, L., eds.), pp. 77–87. Liss, New York.

Haertzen, C.A. and Hooks, N.T. (1969) Changes in personality and subjective experience associated with the chronic administration and withdrawal of opiates. J. Nerv. Ment. Dis. 148, 606–614.

Helzer, J.E. and Pryzbek, T.R. (1988) The co-occurrence of alcoholism with other psychiatric disorders in the general population and its impact on treatment. J. Stud. Alcohol 49, 219–224.

Henningfield, J.E., Chait, L.D. and Griffiths, R.R. (1984) Effects of ethanol on cigarette smoking by volunteers without histories of alcoholism. Psychopharmacology 82, 1–5.

Hill, S.Y., Cloninger, C.R. and Ayre, F.R. (1977) Independent transmission of alcoholism and opiate abuse. Alcohol: Clin. Exp. Res. 1, 335–342.

Johnson, S., Leonard, K.E. and Jacob, T. (1989) Drinking, drinking

styles and drug use in children of alcoholics, depressives and controls. J. Stud. Alcohol 50, 427–431.

Kendler, K.S., Heath, A.C., Neale, M.C., Kessler, R.C. and Eaves, L.J. (1993) Alcoholism and major depression in women: a twin study of the causes of comorbidity. Arch. Gen. Psychiatry 50, 690–698.

Kendler, K.S., Neale, M.C., Kessler, R.C., Heath, A.C. and Eaves, L.J. (1992) Major depression and generalized anxiety disorder: same genes, (partly) different environments? Arch. Gen. Psychiatry 49, 716–722.

Kendler, K.S., Walters, E.E., Neale, M.C., Kessler, R.C., Heath, A.C. and Eaves, L.J. (1995) The structure of genetic and environmental risk factors for six major psychiatric disorders in women: phobia, generalized anxiety disorder, panic disorder, bulimia, major depression, and alcoholism. Arch. Gen. Psychiatry 52, 374–383.

Kessler, R.C., McGonagle, K.A., Zhai, S., Nelson, C.B., Hughes, M., Eshleman, S., Wittchen, H. and Kendler, K.S. (1994) Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Arch. Gen. Psychiatry 51, 8–19.

Klerman, G.L. (1992) Treatments for panic disorder. J. Clin. Psychiatry 53 Suppl., 14–19.

Kosten, T.R., Rounsaville, B.J., Kosten, T.A. and Merikangas, K.R. (1991) Gender differences in the specificity of alcoholism transmission among the relatives of opioid addicts. J. Nerv. Ment. Dis. 179, 392–400.

LaBuda, M.C. and Pickens, R.W. (1995) In: Problems of Drug Dependence, 1994. Proceedings of the 56th Annual Meeting. Vol. II, Abstracts. NIDA Research Monographs 153. DHHS Publication No. 95-3883. Washington D.C. U.S. Government Printing Office, p. 297.

Leonard, B.E. (1994) Serotonin receptors — where are they going? Int. Clin. Psychopharmacol. 9 (Suppl. 1), 7–17.

Lewis, C.E. (1991) Neurochemical mechanisms of chronic antisocial behavior (psychopathy). A literature review. J. Nerv. Ment. Dis. 179, 720–727.

Luthar, S.S., Anton, S.F., Merikangas, K.R. and Rounsaville, B.J. (1992) Vulnerability to substance abuse and psychopathology among siblings of opioid abusers. J. Nerv. Ment. Dis. 180, 153–161.

McGue, M. (1992) When assessing twin concordance, use the probandwise not the pairwise rate. Schizophr. Bull. 18, 171–176.

McGue, M. (1994) Genes, environment and the etiology of alcoholism. In: The Development of Alcohol Problems: Exploring the Biopsychosocial Matrix of Risk (Zucker, R., Boyd, G. and Howard, J., eds.), pp. 1–40. National Institute on Alcohol Abuse and Alcoholism Research Monograph No. 26, US Department of Health and Human Services, Rockville, MD.

McGue, M., Pickens, R.W. and Svikis, D.S. (1992) Sex and age effects on the inheritance of alcohol problems: a twin study. J. Abnorm. Psychol. 101, 3–17.

McGue, M. and Slutske, W. (1993) The Inheritance of Alcoholism in Women, Paper presented at National Institute on Alcohol Abuse and Alcoholism working group for prevention research on women and alcohol, Bethesda, MD.

Mendelson, J.H., Mello, N.K. and Solomon, P. (1968) Small group drinking behavior: an experimental study of chronic alcoholics. In: The Addictive States (Wikler, A., ed.), pp. 399–428. Williams and Wilkins Company, Baltimore.

Merikangas, K.R., Leckman, J.F., Prusoff, B.A., Pauls, D.L. and Weissman, M.M. (1985) Familial transmission of depression and alcoholism. Arch. Gen. Psychiatry 42, 367–372.

Mirin, S.M., Meyer, R.E., McNamee, H.B. and McDougle, M. (1976) Psychopathology, craving, and mood during heroin acquisition: an experimental study. Int. J. Addict. 11, 525–544.

Mirin, S.M., Weiss, R.D., Griffin, M.L. and Michael, J.L. (1991) Psychopathology in drug abusers and their families. Comp. Psychiatr. 32, 36–51.

Noyes, R., Crowe, R.R., Harris, E.L., Hamra, B.J., McChesney, C.M. and Chaudry, D.R. (1986) Relationship between panic disorder and agoraphobia. Arch. Gen. Psychiatry 43, 227–232.

Pickens, R.W., Svikis, D.S., McGue, M., Lykken, D.T., Heston, L.L. and Clayton, P.J. (1991) Heterogeneity in the inheritance of alcoholics: a study of male and female twins. Arch. Gen. Psychiatry 48, 19–28.

Plomin, R. and DeFries, J.C. (1979) Multivariate behavioral genetic analysis of twin data on scholastic abilities. Behav. Genet. 9, 505–517.

Regier, D.A., Farmer, M.E., Rae, D.S., Locke, B.Z., Keith, S.J., Judd, L.L. and Goodwin, F.K. (1990) Comorbidity of mental disorders with alcohol and other drug abuse. J. Am. Med. Assoc. 264, 2511–2518.

Reich, T., Cloninger, C., Lewis, C. and Rice, J. (1981) Some recent findings in the study of genotype-environment interaction in alcoholism. In: Evaluation of the Alcoholic (Meyer, R., ed.), pp. 145–166. NIAAA Research Monograph 5, US Government Printing Office, Washington, DC.

Robins, L.N., Helzer, J.E., Croughan, J., Williams, J.B.W. and Spitzer, R.L. (1981) The NIMH Diagnostic Interview Schedule: Version III, US Public Health Service publication ADM-T pp. 42–44. Washington, DC.

Roe, A. (1944) The adult adjustment of children of alcoholic parents raised in foster homes. Q. J. Stud. Alcohol. 5, 378–393.

Ross, H.E., Glaser, F.B. and Germanson, T. (1988) The prevalence of psychiatric disorders in patients with alcohol and other drug problems. Arch. Gen. Psychiatry 45, 1023–1031.

Rounsaville, B.J., Kosten, T.R., Weissman, M.M., Prusoff, B., Pauls, D.L., Anton, S.F. and Merikangas, K. (1991) Psychiatric disorders in relatives of probands with opiate addiction. Arch. Gen. Psychiatry 48, 33–42.

Rounsaville, B.J., Weissman, M.M., Kleber, H. and Wilber, C. (1982) Heterogeneity of psychiatric diagnosis in treated opiate addicts. Arch. Gen. Psychiatry 39, 161–166.

Schuckit, M. (1986) Genetic and clinical implications of alcoholism and affective disorder. Am. J. Psychiatry 143, 140–147.

Schuckit, M.A. (1979) Alcoholism and affective disorder: diagnostic confusion. In: Alcoholism and Affective Disorders: Clinical, Genetic and Biochemical Studies (Goodwin, D.W. and Erikson, C.K. eds.), pp. 9–19. SP Medical and Scientific Books, New York.

Sellers, E.M., Higgins, G.A. and Sobell, M.B. (1992) 5-HT and alcohol abuse. Trends Pharmacol. Sci. 13, 69–75.

Sellers, E.M., Higgins, G.A., Tomkins, D.M., Romach, M.K. and Toneatto, T. (1991) Opportunities for treatment of psychoactive substance use disorders with serotonergic medications. J. Clin. Psychiatry 52 Suppl., 49–54.

Svikis, D.S. and Pickens, R.W. (1991) Methodological issues in genetic studies of human substance abuse. J. Addict. Dis. 10, 215–228.

Svikis, D.S. and Pickens, R.W. (1994) Genetic aspects of alcohol use in women. Alcohol Health Res. World 18, 192–196.

Van Praag, H.M., Asnis, G.M., Kahn, R.S., Brown, S.L., Korn, M., Harkavy Friedman, J.M. and Wetzler, S. (1990) Monoamines and abnormal behavior. A multi-aminergic perspective. Br. J. Psychiatry 157, 723–734.

Weissman, M.M., Gershon, E.S., Kidd, K.K., Prusoff, B.A., Leckman, J.F., Dibble, E., Hamovit, J., Thompson, W.D., Pauls, D.L. and Guroff, J.J. (1984) Psychiatric disorders in the relatives of probands with affective disorders: the Yale University — National Institute of Mental Health collaborative study. Arch. Gen. Psychiatry 41, 13–21.

Winokur, G. (1979) Alcoholism and depression in the same family. In: Alcoholism and Affective Disorders: Clinical, Genetic, and Biochemical Studies (Goodwin, D.W. and Erikson, C.K., eds.), pp. 49–56. SP Medical and Scientific Books, New York.

Winokur, G. (1982) The development and validity of familial subtypes in primary unipolar depression. Pharmacopsychiatry 15, 142–145.

Winokur, G. and Coryell, W. (1991) Familial alcoholism in primary

unipolar major depressive disorder. Am. J. Psychiatry 148, 184–188.

Winokur, G., Reich, T., Rimmer, J. and Pitts, F.N. (1970) Alcoholism III. Diagnosis and familial psychiatric illness in 259 alcoholic probands. Arch. Gen. Psychiatry 23, 104–111.

Winokur, G., Rimmer, J. and Reich, T. (1971) Alcoholism IV: is there more than one type of alcoholism? Br. J. Psychiatry 118, 525–531.

Winokur, G., Tsuang, M.T. and Crowe, R.R. (1982) The Iowa 500: affective disorder in relatives of manic and depressed patients. Am. J. Psychiatry 139, 209–212.

Woody, G.E., O'Brien, C.P. and Rickels, K. (1975) Depression and anxiety in heroin addicts: a placebo-controlled study of doxepin in combination with methadone. Am. J. Psychiatry 132, 447–450.