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Co-morbidity and familial aggregation of alcoholism and anxiety disorders

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ABSTRACT

Background. This study examined the patterns of familial aggregation and co-morbidity of alcoholism and anxiety disorders in the relatives of 165 probands selected for alcoholism and/or anxiety disorders compared to those of 61 unaffected controls.

Methods. Probands were either selected from treatment settings or at random from the community. DSM-III-R diagnoses were obtained for all probands and their 1053 first-degree relatives, based on direct interview or family history information.

Results. The findings indicate that: (1) alcoholism was associated with anxiety disorders in the relatives, particularly among females; (2) both alcoholism and anxiety disorders were highly familial; (3) the familial aggregation of alcoholism was attributable to alcohol dependence rather than to alcohol abuse, particularly among male relatives; and (4) the pattern of co-aggregation of alcohol dependence and anxiety disorders in families differed according to the subtype of anxiety disorder; there was evidence of a partly shared diathesis underlying panic and alcoholism, whereas social phobia and alcoholism tended to aggregate independently.

Conclusions. The finding that the onset of social phobia tended to precede that of alcoholism, when taken together with the independence of familial aggregation of social phobia and alcoholism support a self-medication hypothesis as the explanation for the co-occurrence of social phobia and alcoholism. In contrast, the lack of a systematic pattern in the order of onset of panic and alcoholism among subjects with both disorders as well as evidence for shared underlying familial risk factors suggests that co-morbidity between panic disorder and alcoholism is not a consequence of self-medication of panic symptoms. The results of this study emphasize the importance of examining co-morbid disorders and subtypes thereof in identifying sources of heterogeneity in the pathogenesis of alcoholism.

INTRODUCTION

Association between alcoholism and anxiety

An association between alcoholism and the anxiety disorders has been observed in both clinical and epidemiological samples (see reviews of George *et al.* 1990*a*; Kushner *et al.* 1990; Wesner, 1990; Schuckit & Hesselbrock, 1994; Crowley & Riggs, 1995). The strength of this association in recent large-scale epidemiological studies suggests that co-morbidity between alcoholism and anxiety states is not attributable to an increased frequency of treatment-seeking among those with co-morbidity (Helzer & Pryzbeck, 1988; Regier *et al.* 1990; Angst, 1993; Kessler *et al.* 1996). However, the nature of this association remains unclear, largely because of the heterogeneity of both disorders and partly as a result of the disparate methodologies employed among the studies that have been conducted so far.

Studies that have investigated co-morbidity according to specific subtypes of anxiety and alcoholism reveal that the association is greater

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for phobic disorders than for panic and generalized anxiety states, and for alcohol dependence than for abuse (Mullaney & Trippett, 1979; Bowen *et al.* 1984; Smail *et al.* 1984; Stockwell *et al.* 1984; Hesselbrock *et al.* 1985; Roelofs, 1985; Weiss & Rosenburg, 1985; Chambless *et al.* 1987; Helzer & Pryzbeck, 1988; Ross *et al.* 1988; Kushner *et al.* 1990; Regier *et al.* 1990; Kessler *et al.* 1996). However, Schuckit & Hesselbrock (1994) concluded that the rates of co-morbid primary anxiety disorders and alcoholism do not significantly exceed population base rates of these disorders.

Comorbidity in family study data

Although the familial aggregation of both alcoholism (Cotton, 1979; Merikangas, 1990*a*; McGue, 1994; Merikangas *et al.* 1994) and anxiety disorders (Carey & Gottesman, 1981; Torgersen & Philos, 1986; Skre *et al.* 1994; Woodman & Crowe, 1996) has been demonstrated in numerous studies, only a few have systematically and simultaneously examined the patterns of co-aggregation of both of these disorders among first-degree relatives of affected probands. Numerous family studies of both alcoholism and anxiety disorders have reported elevated rates of the other condition among relatives (Cohen *et al.* 1951; Noyes *et al.* 1978; Munjack & Moss, 1981; Harris *et al.* 1983; Leckman *et al.* 1983; Merikangas *et al.* 1985). The classic family study of neurocirculatory asthenia by Cohen and colleagues (1951) revealed increased rates of alcoholism among the fathers and brothers of patients compared with those of controls. Indeed, Cohen and colleagues (1951) considered alcoholism as a *forme fruste* of neurocirculatory asthenia, believed to be equivalent to the contemporary concept of panic disorder. However, because comorbidity was not the major focus of these studies, the rates of co-morbid disorders among the relatives were not presented according to comorbidity in the proband. Without such stratification, one cannot determine whether the disorders were transmitted independently.

After removal of artefactual sources of comorbidity such as exclusive use of uncontrolled clinic-based samples, overlap in diagnostic criteria, or failure to consider the effect of confounding factors which may induce comorbidity (e.g. gender), the two possible mechanisms for associations between disorders are: (1) common aetiology, with the index and co-morbid disorders representing alternative manifestations of the same underlying factors, or different stages of the same disease; and (2) causal, in which an index disorder 'causes', or predisposes to the development of the co-morbid disorder.

The chief methods for examining mechanisms for co-morbidity are prospective longitudinal studies of the stability, order of onset and course of co-morbid disorders, treatment studies that discriminate differential treatment response by patterns of co-morbidity, and family and twin studies which examine whether co-morbidity is attributable to common familial or genetic factors. The present study employs the family study method to discriminate between alternative mechanisms for the co-occurrence of two or more disorders by examining patterns of expression of co-morbid and non-co-morbid forms of the disorders among the relatives of probands with co-morbid and non-co-morbid disorders (Merikangas, 1990*b*).

If the two disorders were manifestations of common underlying risk factors, relatives of probands with either disorder alone should have elevated rates of the other disorder alone as compared with expected population rates. Therefore, relatives of probands with anxiety alone should have an increased risk of alcoholism alone and the converse. In contrast, if the relationship between two disorders were aetiological (one condition causing the other) it would be expected that relatives would manifest an increased risk of the causal disorder and the combination of the two syndromes, but not the other disorder alone.

In order to discriminate between these alternatives, family studies must include sufficient numbers of probands with each of the disorders under investigation without a history of the other conditions, and a sample of controls without either of the disorders under study in order to estimate the differences in rates of disorders among the relatives of affected probands *versus* controls using similar sampling and diagnostic procedures.

There are few family studies which were designed specifically to investigate patterns of co-morbidity. We have previously employed family study data to address mechanisms for

co-morbidity of depression and migraine (Merikangas *et al*. 1988) as well as alcoholism, anxiety and depression (Merikangas *et al*. 1994).

Background to the present study

Application of the family study method to our previous work which examined the co-morbidity and co-aggregation of alcoholism, anxiety and depression in a family study of depression with secondary anxiety or alcoholism, yielded evidence for the aggregation of alcoholism and anxiety as well as evidence for the co-aggregation of both disorders within families (Merikangas *et al*. 1994). In a similar study, Maier and colleagues (1993; Maier & Merikangas, 1994) concluded that there are shared susceptibility factors for alcoholism and panic based on an elevated risk of alcoholism among the relatives of probands with pure panic disorder.

METHOD

Sample characteristics

A total of 226 probands were selected from outpatient speciality clinics for alcoholism and/or anxiety disorders at the Connecticut Mental Health Center (New Haven, Connecticut) or through a random digit dialling procedure in the greater New Haven area. The probands were assigned to one of four lifetime diagnostic groups based on an algorithm designed to reflect predominant level of psychopathology: 47 probands and a DSM-III-R diagnosis of alcohol dependence with a DSM-III-R anxiety disorder; 42 probands with a DSM-III-R diagnosis of alcohol dependence without an anxiety disorder; 76 probands with a DSM-III-R diagnosis of anxiety disorders; and 61 normal controls with no lifetime history of a DSM-III-R Axis I disorder. Assignment to the anxiety groups was based on the presence of either DSM-III-R panic disorder with or without agoraphobia or social phobia. Probands assigned to alcohol groups must have had alcohol dependence for at least 1 year with an age of offset greater than 25 years of age in order to rule out episodic experimentation during the high-school, college and post-college years.

Based upon review by clinicians with expertise in substance abuse, probands were excluded from the study if there was evidence of significant organic mental impairment, schizoaffective disorder, schizophrenia or a significant history of drug dependence, particularly intravenous drug use. Probands with a lifetime history of drug abuse or dependence that overshadowed that of alcoholism (e.g. based on an algorithm taking into consideration substance of choice, age of onset, duration, severity, number of symptoms, quantity, frequency and chronicity) were assigned to a separate diagnostic group and will be analysed separately in conjunction with a series of probands in treatment for drug abuse (e.g. marijuana, cocaine and/or opioid abuse/dependence). The normal controls were recruited using a random digit dialling procedure in which they were drawn from the same general population as those of the affected probands. The control group was subjected to the same protocol as the treatment groups. They were considered to be controls if there was no evidence of DSM-III-R psychopathology. The rationale for including a combination of clinically referred probands and those recruited at random from the community was to minimize bias associated with treatment-seeking (e.g. Berkson's bias). All probands were interviewed directly according to the procedures described below.

Interview procedures

Probands

Direct interviews were conducted with all probands and a pedigree was generated that identified spouses, ex-spouses with whom probands have children and first-degree biological relatives. The proband also provided family history information on all his/her first-degree relatives. Permission to contact first-degree relatives as well as their addresses and phone numbers was obtained at the initial interview.

An independent interviewer, blind to the diagnosis of the proband, was then assigned to contact the spouse or first-degree relatives of the proband. Children of the proband under age 18 were enrolled in a longitudinal high-risk component of the study using parallel as well as additional measures. Relatives were directly interviewed either by telephone or in person. In general, studies that have compared the reliability of telephone *versus* personal interviews have found that there was no significant difference in reporting in the two types of interviews (Colombotos, 1969; Aneshensel *et al*. 1982; Weeks *et al*. 1983). Hochstim (1963)

found that the telephone interview may even be more reliable than direct interviews when the questions are comprised of socially undesirable topics, such as drinking behaviour. Indeed, Rohde (1997) found excellent agreement between face-to-face and telephone interviews for the diagnoses of anxiety disorders (kappa = 0·87); major depression (kappa = 0·96) and substance use disorders (kappa = 1·0).

Relatives

The total sample used for the familial aggregation analyses included 224 probands who had 1053 adult first-degree relatives. Approximately equal proportions of relatives were interviewed across proband groups. Entry criteria required that at least one relative and child under 18 participate. Sixty-five per cent (80% parents, 30% siblings and 90% offspring) of the relatives of probands who met study criteria were interviewed directly. Fifty-six per cent of the relatives were queried face-to-face. These rates did not differ significantly by proband diagnostic group and are in accordance with previous family studies of psychiatric disorders (Weissman *et al.* 1986; Mirin *et al.* 1991), and generally compare favourably with previous family studies of alcoholism. The refusal rate for participation of first-degree relatives was approximately 20%. Biases resulting from lack of consent of probands in family studies are discussed by Norden *et al.* (1995). Interview status was controlled in the analytic models presented below.

Diagnostic assessments

Direct interview

The diagnostic interview for adults was the semi-structured Schedule for Affective Disorders and Schizophrenia (SADS), current and lifetime version (Endicott & Spitzer, 1978), which was modified to obtain DSM-III and DSM-III-R criteria (American Psychiatric Association, 1980, 1987). The major modifications of this instrument include: (*a*) addition of an open-ended section designed to obtain a more close approximation of the clinical interview, to facilitate rapport between the interviewer and subject and to identify key diagnostic sections to be completed; (*b*) addition of questions on the inter-relationships of disorders in terms of temporal sequence and shared symptomatology (for subjects meeting less than full criteria); (*c*) elicitation of information on psychiatric disorders and subthreshold manifestations for multiple diagnostic systems; and (*d*) expansion of the substance abuse section to obtain more detailed information on the patterns of use of each drug class, their inter-relationships, and on the course of substance use and abuse. Each diagnostic section of the instrument contained a question regarding whether co-morbid symptoms occurred exclusively in the context of drinking.

Family history information

The method employed for obtaining information on the family history of psychiatric disorders was the Family History-Research Diagnostic Criteria (FH-RDC) developed by Andreasen and colleagues for the collaborative family study of affective disorders (Andreasen *et al.* 1977). The interview, which was modified to enable collection of DSM-III and DSM-III-R criteria, is comprised of the following sections: questions regarding the degree of familiarity and contact with the index relative; an open-ended summary of the history of emotional and behavioural problems and social adjustment of the index relative or spouse; and key probes regarding each major diagnostic area of the DSM-III-R, Axis I adult disorders, antisocial personality disorder, and history of childhood disorders including conduct disorder, attention deficit hyperactivity disorder, and childhood anxiety. Symptoms, severity, impairment, age at onset and treatment history were obtained regarding each syndrome for which the key phenomenological probe was endorsed. The reliability of the diagnostic interview has been investigated by comparing the results of direct interviews of the index person to those obtained by family history. The kappa values for substance abuse and behaviour disorders are in the excellent range, whereas those for specific emotional disorders are acceptable, but far less reliable than those for more observable behaviours.

Training and reliability of interviewers

The interviewers were either psychologists or psychiatric social workers with clinical experience in psychiatric settings. Extensive effort was devoted to establishing the reliability of the diagnostic assessments in several phases of

variable length until satisfactory levels of agreement were obtained. Kappas derived from joint ratings of individual interviews were generally higher for substance abuse (0·72–0·94) than for anxiety or affective disorders which ranged from (0·54–0·78) across the first three series of training sessions.

Diagnostic procedures

The final diagnoses were based upon all available information, including the diagnostic interview, family history reports, and medical records using a best estimate diagnostic procedure. Age of onset of each disorder was defined as the age at which the criteria for the disorder were first met. Although retrospective information was used to estimate ages of onset of diagnostic criteria for each disorder, treatment records and family reports were often used for corroboration to enhance the reliability of the estimates. At a minimum, this ancillary information could clarify the temporality of the onsets of alcoholism and anxiety disorders.

Statistical analysis

Data analysis included standard chi-square tests for two-way tables of categorical level variables and analyses of variance for continuous data. In order to reduce Type I error, a Bonferroni multiple comparison procedure was utilized whereby an alpha level of 0·0063 was determined. Comparisons with significance levels from 0·10 to 0·006 are noted as trends.

The multi-way contingency tables for the association between diagnoses in probands and relatives were analysed via logistic regression. This type of categorical analysis allows an independent assessment of the contribution of several potential predictors on a binary outcome variable, such as the presence or absence of a specific diagnosis. The main effects of the following variables on the risk of alcoholism and anxiety in relatives were examined: (*a*) alcoholism in proband; (*b*) anxiety disorders in proband; (*c*) sex of proband; (*d*) presence of co-morbid disorders in relatives (anxiety disorders for models to predict alcoholism in relatives; alcoholism for models to predict anxiety in relatives); (*e*) sex of relative; (*f*) age of relative (continuous); and (*g*) interview status of relative (direct interview *v*. family history information). Interaction terms involving proband and relative co-morbid diagnoses as well as the gender and co-morbid diagnoses of relatives on the outcome of alcoholism were also examined.

Proportional hazard models

The risk for psychiatric disorders in relatives according to the presence of disorders in probands was calculated using proportional hazard (PH) models, which are general quasi-parametric models (Kaplan & Meier, 1958; Cox, 1972; Bishop *et al.* 1975) where the anti-logarithm of the β and its confidence limits yields a hazard ratio and its confidence limits, which are interpreted as relative risks. The PH procedure yields the regression coefficient β (and its standard error) of an independent variable in estimating the age-specific incidence of the outcome variable (i.e. diagnosis of relatives) while simultaneously controlling for other independent variables which may be related to the outcome. In these models, the age of onset of alcoholism in relatives was used as the dependent variable. If the age of onset was pending, the age at assessment was used as the survival time for the censored observations. The model for alcohol dependence considers dependence onset as the event of interest, with abusers and non-alcoholics as censored outcomes. The model for alcohol abuse considers abuse onset to be the event of interest, with non-alcoholics as censored outcomes and those with alcohol dependence excluded. The age of the relatives was maintained in the models to assess a potential cohort effect. The computer analyses were conducted using the PHREG procedure for proportional hazard models from the Statistical Analysis System (Reinhardt, 1980).

Cumulative logit models

A logistic regression model for ordered categorical outcomes with more than two levels called a cumulative logit model was also applied (McCullagh, 1980) because the outcome variable (alcoholism) could also be categorized ordinally from the least to the most severe: normal, alcohol abuse, alcohol dependence. Rather than modeling the log-odds at a given response level, the cumulative logit models the log-odds of a response less than or equal to a given level. The model incorporates the order of the response levels without giving them arbitrary numerical values of questionable validity. A common slope

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but different intercepts are estimated for each of the outcomes, abuse and dependence.

The form of the cumulative logit model for a variable with three ordered outcome levels is an extension of the binary logit:

(1) $\log\{\text{ODDS of being at or below level } j\} = \theta_j - \beta'\mathbf{X}$

where $j = 1,2$ for first and second outcome levels respectively (dependence, abuse),
$\mathbf{X}$ = covariates (e.g. normal *v.* affected proband),
β = rate of change in log ODDS per unit change in covariate (e.g. normal = 0 *v.* affected = 1),
θ_j = log ODDS of being at or below level j where $\mathbf{X} = 0$ (baseline).

The model shown above (1) is known as the proportional-odds model because the log odds ratio between two values of X, say X_1 and X_2, is proportional to $X_1 - X_2$ and is independent of the level j:

$$\log\{\text{ODDS RATIO of being at or below level } j \text{ when } \Delta X = X_1 - X_2\}$$
$$= (\theta_j - \beta' X_1) - (\theta_j - \beta' X_2)$$
$$= (\theta_j - \theta_j) - \beta'(X_z - X_2)$$
$$= -\beta'(X_1 - X_2).$$

Similar to the proportional hazard models, a significant association between proband anxiety and alcoholism in the relative is consistent with common risk contributing to the two conditions, whereas a lack of an association is consistent with a causal association between the two disorders.

RESULTS

1 Characteristics of the probands

Demographic characteristics of the probands are presented in Table 1. Although there were no significant differences in age across the four diagnostic groupings, there were more females in the anxiety disorder group and fewer females in the alcohol group ($\chi^2 = 43{\cdot}1$, df = 3, $P < 0{\cdot}0001$). The distribution of probands by recruitment source (i.e. treatment *v.* community ascertained) was such that approximately 50% of the subjects with anxiety disorders and approximately 20% of the alcohol groups were ascertained through random digit dialling. No significant differences emerged in the rates of the major diagnostic categories derived from in-person compared to telephone interviews. Alcoholics with or without anxiety disorders were more likely to be divorced at the time of the interview ($\chi^2 = 45{\cdot}2$, $P < 0{\cdot}0001$), and have lower socioeconomic status ($\chi^2 = 35{\cdot}1$, $P < 0{\cdot}0001$).

Probands with a lifetime history of co-morbid antisocial personality or major depression were not excluded from the study. Rather, the effects of these conditions on the association between alcoholism and anxiety in the probands and relatives were examined in multivariate analyses. Approximately 50% of the probands had a current alcohol disorder and 32% had a current diagnosis of social phobia or panic disorder. Eighty-three per cent of the probands with social phobia and alcoholism developed social phobia prior to alcoholism. In contrast, only 47·4% of probands developed panic disorder prior to alcoholism.

2 Unadjusted rates of disorders in relatives by proband diagnostic group

Diagnoses in relatives are presented by proband diagnostic group and sex of relative in Table 2. The diagnoses in relatives are not mutually exclusive with the exception of alcohol abuse and dependence as well as bipolar and unipolar depression. In general, higher rates of the anxiety disorders and affective disorders were observed among the female relatives of affected probands, whereas the rates of alcoholism were higher among the male relatives of affected probands.

Rates of alcoholism were higher in the relatives of probands with alcoholism and anxiety disorder as well as alcoholism alone compared with those of controls ($\chi^2 = 36{\cdot}3$, df = 3, $P < 0{\cdot}0001$). Rates of alcohol dependence but not abuse were significantly greater among relatives of probands with either alcoholism alone or alcoholism plus anxiety ($\chi^2 = 34{\cdot}6$, df = 3, $P < 0{\cdot}0001$). When the rates were examined separately by sex of relative, the male relatives of probands with alcohol and anxiety or alcohol only had significantly higher rates of alcoholism than the male relatives of the anxiety probands ($\chi^2 = 8{\cdot}3$, df = 3, $P < 0{\cdot}01$) and normal controls ($\chi^2 = 20{\cdot}9$, df = 3, $P < 0{\cdot}0001$). These findings were similar for females although it was only marginally significant for relatives of alcoholics

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Table 1. *Description of the proband sample*

Sociodemographic characteristics	Disorders in probands: Alcoholism and anxiety disorders $N = 47$	Alcoholism $N = 42$	Anxiety disorders $N = 76$	Controls $N = 61$	P
Sex Males (%)	55	88	26	43	< 0·001
Socio-economic status (%) Hollingshead† > 3	50	56	28	25	0·001
Marital status (%) Married/remarried	53	66	86	96	< 0·001
Single	4	5	3	2	
Divorced	34	29	12	2	
Source (%) Clinics	85	79	53	—	NS
First-degree relatives ($N = 1053$)	230	195	359	269	NS

† 1,2 = Upper *v.* 3–5 = Lower.

Table 2. *Unadjusted rates of disorders in relatives by proband diagnostic group and sex of relative*

	Disorders in probands: Alcoholism and anxiety disorders			Alcoholism			Anxiety disorders			Controls			Significance		
Sex of relatives Relatives (N)	M 103	F 127	Total 230	M 103	F 92	Total 195	M 177	F 182	Total 359	M 139	F 133	Total 269	M	F	Total
Disorders in relatives															
Alcoholism (All)	48	26	36	47	16	33	33	15	24	24	4	14	***	***	***
Abuse	11	11	11	17	6	12	12	7	10	13	2	7	NS	*	NS
Dependence	37	16	25	30	10	21	21	8	14	12	2	7	***	**	***
Anxiety disorders (All)	13	34	24	16	21	18	18	36	27	16	15	16	NS	***	**
Panic	0	10	5	2	1	2	2	12	7	0	2	1	NS	***	***
Social phobia	9	17	13	6	9	7	8	17	13	7	7	7	NS	*	*
Agoraphobia (±panic)	0	9	5	2	3	3	1	11	6	1	4	2	NS	*	+
Generalized anxiety	5	20	13	6	9	7	11	21	16	7	6	6	NS	**	***
Simple phobia	3	11	7	4	6	5	4	11	7	2	5	4	NS	NS	NS

+ $P < 0·10$; * $P < 0·05$; ** $P < 0·01$; *** $P < 0·001$.

v. anxiety probands ($\chi^2 = 3·03$, df = 3, $P < 0·10$) and normal controls ($\chi^2 = 11·9$, df = 3, $P < 0·001$).

Rates of anxiety disorders in general as well as specific anxiety disorders were significantly greater among relatives of probands with anxiety themselves compared with relatives of those without anxiety (e.g. alcoholism alone, controls). Significant differences in the rates of generalized anxiety disorder and panic disorder in relatives occurred across proband groups. However, these differences were primarily limited to female relatives. With the exception of the trends observed for dysthymia and bipolar disorder, anxiety and affective disorders in male relatives were not associated with anxiety or alcoholism in probands. There was an increase in the rates of bipolar disorder among the male relatives of probands with alcoholism alone. Rates of affective disorders and antisocial personality were elevated among the relatives of all affected probands.

Ages of onset (i.e. age at which full diagnostic criteria were met) were examined among relatives

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Table 3. *Co-morbidity of alcohol dependence and psychiatric disorders in male and female relatives (adjusted odds ratios ±95% confidence limits controlled for age and interview status)*

Sex of relative	Alcoholism				
	Male		Female		
	Dependence	Abuse	Dependence	Abuse	Total
Anxiety (All)	2·0 (1·2–3·3)**	1·6 (0·7–3·5)	3·7 (1·9–7·0)***	0·7 (0·3–1·7)	2·5 (1·7–3·7)***
Panic disorder	0·6 (0·1–5·2)	3·4 (1·1–10·0)*	4·2 (1·8–9·8)***	1·2 (0.1–11.0)	2·7 (1·2–5·8)*
Generalized anxiety	2·3 (1·1–4·5)*	1·6 (0·6–4·4)	2·8 (1·4–5·7)**	0·4 (0·1–1·9)	2·5 (1·5–4·1)***
Social phobia	1·7 (0·8–3·4)	2·1 (0·8–5·6)	4·1 (2·0–8·6)***	0·4 (0·1–1·7)	2·4 (1·5–4·0)***
Agoraphobia	—	5·0 (1·7–14·2)**	2·4 (0·9–6·2)	5·0 (0·7–36·6)	1·5 (0·6–3·8)
Affective (All)	5·2 (3·2–8·5)***	2·6 (1·2–5·7)*	5·3 (2·7–10·2)***	1·3 (0·6–2·9)	5·1 (3·5–7·6)***
Major depression	5·5 (3·1–9·6)***	1·9 (0·8–4·6)	2·1 (1·1–4·3)*	1·2 (0·4–3·3)	3·6 (2·3–5·5)***
Bipolar disorder	2·4 (0·4–14·6)	13·0 (2·4–695)**	9·6 (2·8–33·4)***	11·2 (1·0–128·0)*	5·8 (2·0–16·4)***
Dysthymia	3·7 (1·8–7·6)***	1·3 (0·4–3·9)	3·4 (1·7–7·0)***	0·7 (0·2–3·2)	3·5 (2·1–5·8)***
Substance abuse or dependence	10·5 (5·0–21·9)***	2·2 (0·6–7·7)	13·1 (4·9–35·3)***	6·0 (1·6–22·5)**	10·6 (5·8–19·6)***
Antisocial personality	34·5 (7·9–151·7)***	22·1 (1·9–26·0)*	36·8 (9·0–149·8)***	—	36·3 (13·2–100·3)***

NB: These are non-mutually exclusive diagnoses.
* $P < 0·05$; ** $P < 0·01$; *** $P < 0·001$.

who had a specific anxiety disorder and alcoholism. Approximately 74% of relatives with social phobia and alcoholism developed social phobia prior to alcoholism. In contrast, only 12·5% of relatives developed panic disorder prior to alcoholism.

3 Co-morbidity in relatives

Table 3 provides the sex-specific odds ratios adjusted for age and interview status of the relative for the co-occurrence of anxiety and affective disorders with alcohol dependence in relatives. Differential risks for the co-occurrence of these disorders exist between males and females, with the exception of dysthymia and antisocial personality disorder. The risk of co-morbid anxiety and alcohol dependence was higher in females, whereas the co-occurrence of major depression and alcohol dependence appeared higher in males.

4 Multivariate modelling of co-morbidity and co-transmission

Alcoholism and anxiety

In order to control for multiple potential confounders in the simultaneous investigation of the co-aggregation and co-morbidity of alcoholism and anxiety disorders, proportional hazard models were applied to the data. Covariates previously identified as important in earlier family studies of alcoholism and psychopathology were included in these analyses (i.e. sex of proband and sex, age, and interview status of relative). The specificity of familial aggregation of alcoholism and anxiety disorders in relatives was examined by inclusion of the corresponding disorder in probands, while cross-aggregation was examined simultaneously by the inclusion of the alternate disorder in the probands. For the prediction of alcohol disorders in relatives, co-morbidity within the relatives was included in the models.

Alcohol dependence in the proband was significantly associated with alcohol dependence in relatives, after controlling for proband anxiety, anxiety in the relative, interview status, sex and age of the relative. The association between these two factors was stronger in models in which the alcohol case definition in the relatives was subset to alcohol dependence (risk ratio = 2·8, $P < 0·0001$) and in this case an anxiety disorder (risk ratio = 1·5, $P < 0·04$) in the proband was also significantly associated with alcohol dependence in the relative (Table 4). Consistent with the bivariate associations, the rate of co-morbidity of anxiety disorders and alcohol dependence was higher in female relatives (risk ratio = 3·6, $P < 0·0002$). The risk of alcoholism was found to decrease with increasing age of relative (earlier birth cohort) and males were more likely to be alcoholic than females (risk ratio = 3·6, $P < 0·0001$).

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Alcoholism and specific anxiety disorders

In order to examine the co-transmission of the two major anxiety disorders (i.e. social phobia and panic), mutually exclusive categories were created for probands based upon fulfilment of diagnostic criteria for these specific disorders and anxiety group assignment (i.e. social phobia and panic, social phobia, panic, other anxiety and none).

Table 4. *Co-morbidity and co-aggregation of alcohol dependence and abuse and anxiety disorders among probands and relatives*: *results of proportional hazard models*

	Alcoholism in relatives (hazard ratios ± 95% CI)	
Factors in models	Alcohol dependence ($N = 996$)	Alcohol abuse ($N = 821$)
Disorders in probands		
Alcohol dependence *v.* Not	2·83 (2·0–4·0)***	1·61 (0·94–2·8)$^{+}$
Anxiety *v.* Not	1·46 (1·0–2·1)*	0·99 (0·59–1·6)
Disorders in relatives		
Anxiety *v.* Not	2·07 (1·4–3·0)***	0·89 (0·53–1·6)
Covariates for relatives		
Interviewed *v.* Not	1·24 (0·83–1·8)	1·81 (1·0–3·1)*
Age (current in years)†	0·98 (0·97–0·99)***	0·96 (0·94–0·98)***
Female *v.* Male	0·28 (0·19–0·41)***	0·42 (0·25–0·71)**
Covariates for probands		
Female *v.* Male	1·43 (0·99–2·1)	0·91 (0·53–1·5)

† Increase per year.
‡ Analyses controlling for antisocial personality disorder and major depression in probands yielded similar results.
$^{+}$ $P < 0·1$; * $P < 0·05$; ** $P < 0·01$; *** $P < 0·001$.

Table 5. *Co-morbidity and co-aggregation of alcohol dependence and specific anxiety disorders among probands and relatives* (*hazard ratios* ± 95% *CI*)†

	Alcohol dependence in relatives ($N = 996$)
Factors in models	Hazard ratios (CI)
Disorders in probands	
Alcohol dependence *v.* Not	3·01 (2·1–4·3)***
Panic disorder	1·63 (1·1–2·4)**
Social phobia	0·99 (0·69–1·4)
Disorders in relatives	
Panic disorder	1·44 (0·71–2·9)
Social phobia	1·87 (1·2–3·0)**
Covariates for relatives	
Interviewed *v.* Not	1·22 (0·82–1·8)
Age	0·98 (0·97–0·99)***
Female *v.* Male	0·28 (0·19–0·42)***
Covariates for probands	
Females *v.* Male	1·37 (0·94–2·0)

† Analyses controlling for co-morbid antisocial personality disorder and major depression in the proband yielded similar results.
** $P < 0·01$; *** $P < 0·001$.

In proportional hazard models (Table 5) which included panic disorder and social phobia, both alcohol dependence (risk ratio = 3·01, $P < 0·0001$) and panic disorder (risk ratio = 1·63, $P < 0·01$) in the proband independently increased the risk of alcohol dependence in relatives, whereas social phobia in the proband was not associated with an increased the risk of alcohol dependence in relatives (risk ratio = 0·99, NS). Panic in the relatives was not associated with alcohol dependence whereas relative sex and age were significantly associated with alcohol dependence.

Because of the low base rates of anxiety disorders in male relatives, we examined subthreshold cases, defined as meeting the key diagnostic probe as well as full symptom criteria, but excluding the duration and impairment criteria (Angst *et al*. 1997). This yielded a strong association between alcohol dependence and panic in both genders. Adjusting for major depression and generalized anxiety in probands changed neither the parameter estimates nor conclusions regarding statistical significance. Additional analyses controlling for antisocial personality disorder in the relatives did not affect the relationship between alcoholism in the probands and alcoholism and/or anxiety disorders in the relatives. In order to determine whether the results were stable across recruitment source (e.g. clinic *v.* community ascertainment) and interview mode (direct in-person *v.* telephone) we entered a dummy variable into the analyses. The results showed that neither recruitment source nor interview mode were confounders of the relationship between alcoholism and/or anxiety disorders in the family transmission analyses.

Simultaneous assessment of alcohol abuse and dependence

The final multivariate models used to examine these data were cumulative logit models. In this type of model, alcohol abuse and dependence were examined simultaneously by treating them as ordinal outcomes with dependence considered

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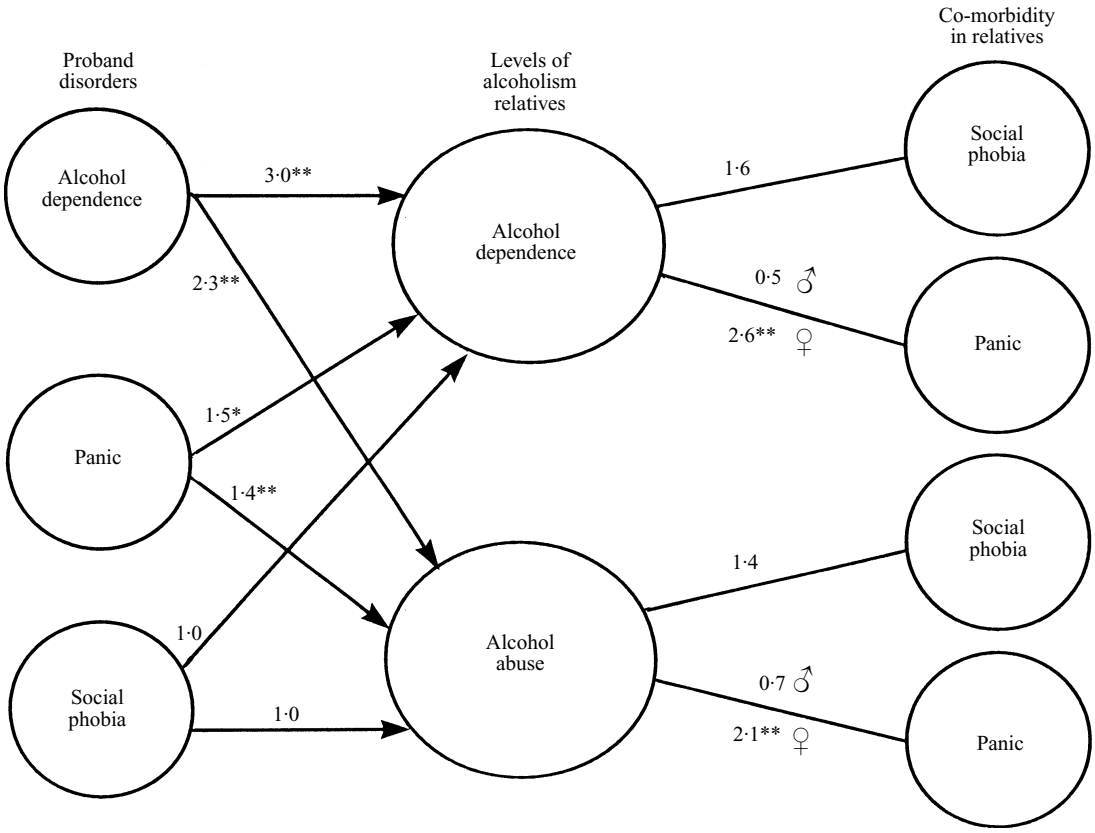

FIG. 1. Adjusted odds ratios of levels of alcoholism (abuse/dependence) of relatives from cumulative logit models of alcoholism and anxiety in probands and relatives. The 95% confidence limits are: proband alcohol dependence–relative alcohol dependence (2·2, 4·2); proband panic–relative alcohol dependence (1·1, 2·2); proband social phobia–relative alcohol dependence (0·7, 1·4); proband alcohol dependence–relative alcohol abuse (1·8–3·1); proband panic–relative alcohol abuse (1·1, 1·8); proband social phobia–relative alcohol abuse (0·85, 1·26). For relatives: relative social phobia–alcohol dependence (1·0, 2·6); relative panic–relative alcohol dependence (0·1, 2·8) male – (1·2, 5·5) female; relative panic–relative alcohol abuse (0·43, 2·19) male – (1·15–4·06) female; relative social phobia–alcohol abuse (0·99–2·04).
Each odds ratio controls for: (1) the other six proband and relative diagnoses shown including a panic by sex interaction; and (2) proband sex, relative sex, relative age and interview status. (* $P < 0{\cdot}05$; ** $P < 0{\cdot}01$.)

as a more severe type of alcoholism than abuse. In addition, *a priori* statistical interactions between sex of relative and co-morbid conditions as well as interactions between proband diagnoses were tested. In each case, the goodness-of-fit statistic indicated that the data supported the proportional-odds assumption. The odds ratios from the final model are presented in Fig. 1.

We observed that proband alcohol dependence predicted both alcohol abuse (OR = 2·3) and alcohol dependence (OR = 3·0) in relatives ($\chi^2 = 44{\cdot}4$, df = 1, $P < 0{\cdot}0001$). We also observed that panic disorder in probands predicted alcoholism in relatives (OR = 1·4 for alcohol abuse and OR = 1·5 for alcohol dependence; $\chi^2 = 6{\cdot}2$, df = 1, $P = 0{\cdot}0124$). With respect to co-morbidity in relatives, panic and alcohol disorders were significantly associated in female relatives only (OR = 2·1 for alcohol abuse and OR = 2·6 for alcohol dependence; $\chi^2 = 6{\cdot}2$, df = 1, $P = 0{\cdot}0126$), while social phobia was associated with alcoholism in the overall relative sample (OR = 1·4 for alcohol abuse and OR = 1·6 for alcohol dependence; $\chi^2 = 3{\cdot}6$, df = 1, $P = 0{\cdot}0572$). The addition of affective disorders to the cumulative logit model did not substantially alter our conclusions. Although the statistical significance of the association between social phobia and alcoholism decreased, the effect size

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remained relatively fixed. In order to examine whether interview status was important in influencing the relationship between alcoholism and anxiety as described in the final models, we ran an additional set of analyses using only the directly interviewed relatives. The association between alcoholism and anxiety disorders remained the same.

DISCUSSION

Familial aggregation of alcoholism and anxiety

The results of the present study confirm the well-established familial aggregation of both the anxiety disorders and alcoholism (Cohen *et al.* 1951; Noyes *et al.* 1978; Munjack & Moss, 1981; Harris *et al.* 1983; Leckman *et al.* 1983). There was a three-fold increased risk of alcoholism among the relatives of probands with alcoholism and a two-fold increased risk of anxiety disorders among the relatives of probands with anxiety. However, this study also revealed that the familial transmission of alcoholism can be primarily attributed to alcohol dependence, rather than abuse, thereby validating the DSM-III-R and ICD-10 distinction between alcohol abuse and dependence (Edwards & Gross, 1976). Similar conclusions were drawn from the results of a twin study of Pickens and colleagues (1991) and the longitudinal study of Hasin *et al.* (1990). Although familial transmission of alcohol dependence was far greater than that of abuse in the present study, there was still evidence for transmission of alcohol abuse in female relatives. Hence, the abuse–dependence distinction may be more important in discriminating alcoholism in males than in females.

Previous twin and adoption studies of alcoholism have been inconclusive with respect to the role of genetic factors in the gender differences in alcoholism. Twin studies have suggested greater heritability for early onset male alcoholism than for female alcoholism (McGue *et al.* 1992) and for alcohol dependence than for abuse in women (Pickens *et al.* 1991). In contrast, the most recent large-scale twin study of a population-based sample revealed equal levels of heritability of alcohol dependence among males and females (Heath *et al.* 1997). The study of female twin pairs by Kendler *et al.* (1992) revealed that genetic influences were important for alcoholism for both narrow and broad definitions of alcoholism.

Association between alcoholism and anxiety

The present study confirms the association between alcoholism and anxiety disorders as reported in previous clinical and epidemiological studies (Regier *et al.* 1990; Wesner, 1990; Kessler *et al.* 1996). Our further investigation of potential sex-specific patterns and pathways revealed that these associations between alcohol dependence and anxiety disorders were primarily a function of the effect in female relatives. Otto *et al.* (1992) reported that alcoholism among patients with panic disorder was primarily due to co-morbidity in women. Existing studies have frequently yielded inconsistent results regarding gender-specific co-morbidity (Smail *et al.* 1984; Chambless *et al.* 1987; Otto *et al.* 1992).

In the present study, the association between the specific subtypes of anxiety disorders and alcohol dependence was greater for females than for males, possibly due to the extremely low rates of threshold-level anxiety disorders among the males. As shown in previous studies, we found a more consistent association between alcoholism and social phobia across gender than between alcoholism and panic disorder, for which there was no evidence for co-morbidity in males. However, when repetitive spontaneous panic attacks with full symptomatic criteria were considered, a strong association emerged in both genders. Examination of the sex-specific parameters (without respect to their statistical significance) show that the association is not a function of the relative number of cases in males *v.* females. Different patterns of co-morbidity between alcoholism and specific subtypes of anxiety as well as sex differences may explain the discrepant conclusions regarding co-morbidity between alcoholism and anxiety (Schuckit & Hesselbrock, 1994). However, Schneier *et al.* (1992), Angst *et al.* (1993) and Kessler *et al.* (1997) have all reported associations between alcoholism and social phobia and panic in large-scale epidemiological studies in both men and women.

Inspection of data on retrospective recall of the order of onset of alcoholism and anxiety disorders in the subjects with co-morbidity revealed that the majority of those with social phobia reported the onset of social phobia prior

to that of alcoholism. This concurs with several previous clinical studies in which social phobia tended to precede that of alcoholism in patients with co-morbidity (Mullaney & Trippett, 1979; Bowen *et al.* 1984; Weiss & Rosenburg, 1985; Stravynski, *et al.* 1986). In contrast, similar to the results of previous studies in which there appeared to be no specific pattern of onset of panic with respect to alcoholism (Powell *et al.* 1982; Hesselbrock *et al.* 1985; Chambless *et al.* 1987; Ross *et al.* 1988; George *et al.* 1990); nearly equal proportions of subjects with co-morbid panic disorder and alcoholism reported the onset of panic earlier, simultaneous to, or later than the onset of alcoholism. The findings from retrospective studies were recently confirmed by the results of a prospective longitudinal cohort study of young adults selected from the general community in Zurich, Switzerland in which the onset of panic and alcohol misuse either tended to occur in close temporal proximity or with alcohol misuse preceding the onset of panic (Degonda & Angst, 1993).

Association between alcoholism and specific subtypes of anxiety

The findings of the present study suggest two pathways for co-morbidity between alcoholism and anxiety disorders. The rates of alcoholism were increased only among relatives of social phobics who themselves manifested social phobia. This suggests that the two disorders are transmitted independently despite the large degree of co-morbidity between them. When taken together with the patterns of onset of these conditions reported in this study as well as in numerous other clinical and epidemiological studies, the findings are consistent with a self-medication model in which alcoholism develops as a consequence of social phobia.

In contrast, co-morbidity between panic disorder and alcoholism is partially attributable to shared aetiological factors. The non-systematic patterns of onset of panic and alcoholism suggest that panic and alcohol disorders may represent manifestations of the same underlying risk factors. These findings are remarkably similar to those of Maier and colleagues (1993) who found evidence for increased risk of 'pure' alcoholism in the relatives of probands with 'pure' panic disorder, but no significant symmetric effect for panic disorder in relatives of probands with alcoholism. Indeed, the adjusted odds ratios for the association between alcoholism and panic disorder were nearly identical to those in the present study. However, it is likely that the lack of symmetry results from diminished statistical power. Likewise, in their twin study of females, Kendler *et al.* (1995) found a genetic factor with high loadings on major depression and generalized anxiety disorder that also included modest loadings for both panic disorder and alcoholism. Aside from common genetic factors, shared aetiological factors leading to alcoholism or panic may include common biological or psychosocial environmental risk factors. The manifestation of a particular disorder may be a function of the timing of risk factors and/or additional mediating genetic or environmental factors.

Alcoholism may have differential associations with specific anxiety disorders in that the underlying physiological mechanism or vulnerability involved with each type of disorder may react differently to the anxiolytic properties of alcohol (Kushner *et al.* 1990). Our data suggest that subjects with social phobia admit to using alcohol to assuage anxiety when confronted with the phobic stimulus, confirming the conclusions of several previous clinical studies of both alcoholics and phobics. Subjects with panic disorder were far less likely to report using alcohol for self-medication of anxiety; rather, panic attacks may be precipitated by physiological changes resulting from alcoholism. This could result from differences in the core phenomenology of these anxiety disorders, based on the fairly predictable occurrence of exposure to provocative situations by social phobics, particularly those with specific social phobia, in contrast to the unpredictable occurrence of panic attacks in patients with panic disorder, particularly during the early manifestations of this syndrome.

Strengths and limitations of present study

The strengths of this investigation are the application of a family study design to address specifically mechanisms for co-morbidity, selection of probands from both clinical and community settings to enhance the generalizability of the findings, investigation of co-morbidity and co-aggregation of specific subtypes of these

conditions, and the use of multivariate techniques in order to control for potential confounders. The use of a longitudinal design to investigate the order of onset of psychiatric disorder in the high risk component of this study will help to clarify the order of the onset of these disorders without bias inherent in retrospective recall. In addition, this is the first family study designed specifically to examine co-morbidity of specific subtypes of alcoholism and the specific subtypes of anxiety disorders including both panic disorder and social phobia.

The application of the cumulative logit model for this ordinal response variable (alcoholism) is an important advance over alternative modelling strategies. Use of one model for several different outcome levels yields statistically efficient estimates, allows for direct comparison of effect sizes, and incorporates the order of the outcomes simultaneously on all subjects in the analysis.

The selection of optimal control and comparison groups for family studies has been discussed extensively; selection of controls without psychopathology (i.e. 'super-normal') and probands with 'pure' disorders have been criticized because they may exaggerate the difference between relatives of cases and controls for all psychiatric disorders rather than only the disorder under study (Kendler, 1990). However, Klein (1993) argued that the careful screening of both case and control probands and appropriate multivariate analyses can minimize bias arising from sampling of unaffected controls. Additionally, Hill & Neiswanger (1997) argue that unaffected controls minimize heterogeneity in genetic linkage and association studies. Comparison of the results of the present study using a control group without substance abuse, anxiety or depression, with a control group which included depression (who were excluded from the study) did not alter the findings reported herein. Moreover, the comparability between the rates of disorders in relatives of controls in the present study and those reported in recent epidemiological studies suggests that they comprise an unbiased comparison group (Kessler, *et al*. 1996).

One methodological limitation of the present study is the lack of direct interview data on all of the relatives necessitating the derivation of best estimate diagnoses based on family history information. However, Graham & Jackson (1993) have reported that proxy sources are unlikely to lead to biased estimates of alcohol consumption. Another limitation is the lack of power to investigate specificity and co-morbidity of subtypes of the rarer conditions in this sample, particularly co-morbid disorders not directly under investigation herein.

Implications of findings of the present study

These findings have important implications for the diagnostic classification, and for the course, treatment and prevention of these disorders. As described above, the distinction between alcohol abuse and dependence in the current diagnostic classification systems was validated by our findings.

As highlighted by the originators of the term co-morbidity, characterization of subjects according to all disorders rather than to the presenting disorder or more significant disorder is critical for adequate prediction of course and outcome (Kaplan & Feinstein, 1974). Numerous studies have revealed that the course of substance abuse is worse in the presence of psychiatric disorders (Rounsaville *et al*. 1987). Alcoholics with co-morbid anxiety have been shown to experience more severe alcohol withdrawal, an increased tendency to relapse, greater impairment levels, and worse prognosis than those without anxiety disorders (Johnston, *et al*. 1991; LaBounty *et al*. 1992; Lotufo-Neto & Gentil, 1994).

The co-morbidity of alcoholism and anxiety disorders may also affect the evaluation and treatment of individuals with those conditions, irrespective of the disorder for which they seek treatment. Alcohol disorders resulting from self-medication may often go unrecognized in treatment settings for anxiety disorders. Indeed, alcohol withdrawal can closely mimic the symptoms of panic and generalized anxiety. Moreover, persons with co-morbid anxiety and alcoholism often manifest additional co-morbid disorders, particularly affective disorders. Consequently, it is essential to evaluate potential manifestations of anxiety and depression during alcohol withdrawal and subsequent abstinence when designing long-term treatment strategies (Anthenelli & Shuckit, 1993).

The differential relationships between panic and phobic states with alcoholism are also relevant to the development of alcohol treatment

programmes. Whereas treatment of alcoholics with social phobia should focus on the amelioration of the underlying social phobia using the highly efficacious methods demonstrated for this condition in contemporary psychiatry (Marks & Lader, 1973; Liebowitz *et al*. 1988; Heimberg & Juster, 1995; Potts & Davidson, 1995), treatment of panic in the context of alcoholism could be more appropriately directed at abstinence to determine whether panic attacks are potentiated by ethanol. Treatment strategies that address both conditions may ultimate yield greater efficacy than those that focus solely on the index condition for which the subject sought treatment.

The relationships between alcoholism and anxiety disorders described in this article also provide key information for both primary and secondary prevention of these disorders. A family history of these conditions is an important indicator of an increased risk to the offspring in these families. The potential aetiological pathway from anxiety disorders to alcoholism suggests that children with high levels of anxiety symptoms or anxiety disorders have a heightened risk for the use of alcohol to self-medicate the symptoms of anxiety, particularly in the presence of other known risk factors for the development of alcoholism. The early identification and treatment of these children could help to prevent the development of alcohol abuse and dependence.

Conclusion

These findings illustrate the importance of the use of family studies to investigate the mechanisms underlying co-morbidity. Compared with other experimental approaches, family studies examining high-risk relatives (i.e. relatives of probands with a specific diagnosis) remove some of the selection biases associated with analysing clinical treatment samples and increase the number of potential subjects with the desired co-morbidity. Thus, family studies can produce more stable estimates of the risk of co-morbidity. Twin studies are also a powerful approach to investigate mechanisms for co-morbidity since they permit estimation of the degree to which genetic and environmental factors may contribute to the joint expression of several syndromes (see Kendler *et al*. 1993, 1995).

Finally, these results suggest that family studies of alcoholism should discriminate between families with panic and those with social phobia. In the former case, alcoholism could represent a manifestation of the same underlying diathesis, whereas in the latter case, social phobia would be the chief phenomenon of interest. Clarifying mechanisms for co-morbidity is essential for the accurate classification of subjects for genetic studies, or for any study that seeks to gain understanding of the pathophysiology of alcoholism or anxiety disorders.

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