

RESEARCH REPORT

The life-time rates of three major mood disorders and four major anxiety disorders in alcoholics and controls

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Abstract

Aims. While psychiatric symptoms are common in the general population and even more prevalent in alcoholics, their clinical implications are not clear. The goal of this study was to establish the life-time rates of several independent and concurrent mood and anxiety disorders in alcoholics, controls and their relatives.

Design. Structured interviews were administered to alcoholics entering treatment, their relatives, and controls. **Setting.** The study was carried out in six different centers in the United States as part of the Collaborative Study on the Genetics of Alcoholism (COGA). **Participants.** Data were gathered from 2713 alcohol dependent subjects (probands and their alcoholic relatives) and 919 controls. **Measurements.** The timeline-based Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA) interview was administered face to face by trained, closely supervised interviewers. The life-time rates for concurrent and independent disorders were determined for three DSM-III-R major mood and four major anxiety disorders. **Findings.** Some form of independent mood disorder was seen during the life-time in slightly fewer alcoholics than controls (14.0% and 17.1%), but alcoholics did show higher rates of independent bipolar disorder (2.3% vs. 1.0%). The life-time rate for independent anxiety disorders was significantly higher in alcoholics than controls (9.4% vs. 3.7%), with most of the differential related to panic disorder (4.2% vs. 1.0%) and social phobia (3.2% vs. 1.4%), but no significant group differences for agoraphobia or obsessive-compulsive disorder. In general, these findings regarding mood and anxiety disorders were reflected in close relatives. **Conclusions.** The large majority of alcohol-dependent men and women in this sample did not have any of the independent mood or anxiety disorders evaluated here. However, there was evidence of enhanced risks among alcoholics for independent bipolar, panic and social phobic disorders. Studies which do not distinguish carefully between independent and concurrent mood and anxiety disorders in alcoholics are likely to report much higher rates of co-morbid psychiatric disorders than those that distinguish between the two types of syndromes.

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Submitted 5th December 1996; initial review completed 4th March 1997; final version accepted 20th March 1997.

Introduction

Alcohol dependence (alcoholism) is associated with a high rate of psychiatric symptoms.¹⁻⁹ Whether evaluated through national epidemiological studies or ascertained as a consecutive series of individuals entering treatment, at least two-thirds of alcoholic individuals show substantial symptoms of anxiety, sadness, manic-like conditions, other substance use disorders or severe and pervasive antisocial behaviors. These additional clinical conditions must be recognized, steps are required to help deal with the immediate impact of the symptomatology and it is important to consider the possible need for longer-term pharmacological treatments.

However, there is a great deal of heterogeneity in the psychiatric symptomatology observed among alcohol dependent men and women. First, for some alcoholics the symptoms reflect long-term, major psychiatric disorders which sometimes require life-long therapies. Thus, alcoholics have greater than general population rates for bipolar manic-depressive disease^{6,8,10,11}, schizophrenia¹² and full-blown antisocial personality disorders (ASPD).^{6,13,14} It is possible that the disordered thinking and impulsiveness of these conditions might have contributed to the heavy drinking. There is little disagreement that these major psychiatric disorders often antedated the alcoholism or remained clinically significant following 4 or more weeks of abstinence, in which case the alcoholic is likely to have a prognosis associated with the independent psychiatric syndrome.

A second possibility is that the high rate of psychiatric symptoms among alcohol-dependent men and women might reflect an effort by most to "self-medicate" pre-existing psychiatric symptoms through the use of high doses of alcohol.^{15,16} However, it has been difficult to garner substantial evidence to support this hypothesis, as some studies have reported that pre-existing psychiatric symptomatology rarely improve, and often intensify, in the context of heavy drinking.^{15,19}

A third hypothesis that has been proposed to help explain the high concurrence between alcoholism and psychiatric symptoms is that there might be genetic linkage with alcoholism for at least some characteristics or disorders such as manic depressive disease or ASPD.^{8,10,20} A related possibility reflects assortative mating between alcohol dependent individuals and

mates with other psychiatric disorders, which would increase the risk for both syndromes in the offspring.^{21,22} A fourth set of factors likely to contribute to the co-occurrence of major psychiatric syndromes and alcohol dependence might be a consequence of research methodology, including the increased probability that an individual with more than one psychiatric disorder will be more likely than others to be identified as a clinical case and, thus, be included in a study.²³

This paper evaluates a fifth possible contributor to the relationship between psychiatric symptoms and alcohol dependence, one which occurs through a mechanism which the Fourth Diagnostic and Statistical Manual of the American Psychiatric Association (DSM-IV) refers to as substance-induced disorders.²⁴ Intense intoxication and withdrawal from alcohol are associated with signs and symptoms of depression, anxiety and even psychoses. Conditions that resemble major depressive disorders have been observed during extended drinking experiments,²⁵⁻²⁸ and one-third or more of alcoholics show high levels of depressive symptomatology while drinking and during the first 2-4 weeks following abstinence.^{29,30} Despite the intensity of these depressive episodes, in 80-90% of these individuals the mood states improve and no longer meet criteria for a major depressive disorder with several additional weeks of nondrinking.³⁰⁻³⁵ Similarly, anxiety symptoms resembling generalized anxiety disorder (GAD), phobic problems and panic attacks are common during intoxication and withdrawal from alcohol, but are likely to dissipate over the first several weeks or months following abstinence.³⁶⁻⁴¹

Thus, a substantial proportion of the common and distressing psychiatric syndromes among alcoholics might represent clinically relevant, but temporary, conditions occurring concurrent with the intoxication and withdrawal. Because these symptoms are likely to improve markedly within several weeks of abstinence and continue to diminish over time, these men and women with substance-induced, or concurrent, syndromes might represent an important and unique subgroup of alcoholics for whom the optimal treatments might differ substantially from those most appropriate for individuals with independent psychiatric disorders.

The study methodology required to tease out the proportion of psychiatric syndromes among

alcoholics that reflect each of the five conditions described above is daunting. Epidemiological studies can help by offering accurate descriptions of the rates of symptomatology associated with alcoholism, but often involve such large projects with such little opportunity for supervision of interviewers by clinical researchers that it can be difficult to separate independent from concurrent conditions. At least three excellent large-scale national studies have reported a high prevalence of psychiatric syndromes among alcoholics, but the sheer scope of these projects and the emphasis on epidemiological approaches make it difficult to establish the proportion of individuals with psychiatric syndromes for whom the disorder is independent of intoxication or withdrawal states.¹⁻⁵

Using a second approach, evaluations of alcohol-dependent men and women entering treatment offer the opportunity of more intensive evaluations of each case. However, this method suffers from problems associated with the higher level of severity of illness often observed among these individuals,^{19,23} as well as difficulties inherent in evaluations performed during withdrawal when concurrent and temporary anxiety and depressive states are common.⁶⁻⁸ Thus, while a series of impressive studies of consecutive admissions to clinical programs have supported the high prevalence of psychiatric symptoms among alcohol-dependent men and women^{6,8,14,42}, interviews were often carried out within the first several weeks of abstinence and researchers often did not use a careful time-line to evaluate the clinical course of the various syndromes over time. One study did incorporate a follow-up of subjects over time, documenting stability for the high rates of ASPD, but reported life-time histories of major depressive disorder that did not appear to be a great deal higher than those noted in the general population.¹⁴

The ideal study might combine these assets and liabilities of epidemiological and treatment-based work by incorporating a highly structured diagnostic interview created to facilitate the distinction between independent and concurrent disorders.⁴³⁻⁴⁵ The instrument could then be applied to a large number of alcohol dependent men and women from diverse settings, gathering information from multiple data sources, such as additional informants or treatment records. The perfect study would incorporate a follow-up

component to document clinically relevant changes in symptomatology over time. Unfortunately, no such investigation has yet been carried out.

In an effort to add another incremental step to our to understanding of the relevance of comorbid conditions among alcoholics, this paper presents data from the Collaborative Study of the Genetics of Alcoholism (COGA).⁴⁶⁻⁴⁹ The study has the assets of a large sample of alcohol-dependent men and women and controls, with all individuals evaluated with a structured research instrument that was created using a time-line approach to distinguish psychiatric syndromes that occurred in the context of substance-related disorders from those that appear to have developed independently of alcohol or drug dependence. It is hoped that the information offered here will complement treatment trials and large epidemiological investigations, and offer another perspective on the co-morbidity between substance use disorders and major psychiatric syndromes.

Methods

The COGA investigation is a pedigree study of alcohol-dependent men and women, their relatives and controls. As described in greater detail elsewhere, standard procedures were used to gather information through face-to-face interviews with a consecutive series of alcoholics entering inpatient or aftercare treatment programs in six centers in St Louis, MO, New York, NY, Farmington, CT, Indianapolis, IN, Iowa City, IA and San Diego, CA.^{2,26} The sample of alcoholics reflected 954 original probands and 1759 alcohol-dependent relatives, 79.6% of whom have never had formal treatment.

All probands met criteria for DSM-III-R alcohol dependence,⁵⁰ as well as definite alcoholism as defined by Feighner *et al.*,⁵¹ and all had multiple alcoholic relatives.⁴⁷ Subjects were excluded if they did not speak English, if they had evidence of recent repeated intravenous drug use (in order to decrease heterogeneity), or if fewer than five first-degree relatives were available for evaluation, but there were no exclusions based on co-morbid diagnoses. Controls were selected through different methods at the six centers, including random mailings to students at a university, drivers' license records, as well as individuals receiving care for non-psychiatric

disorders. As usual in COGA analyses, controls are included regardless of their diagnoses.

The Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA) interview⁴⁸ was used to evaluate probands, all available first-degree and extended relatives, controls and their relatives. This highly structured diagnostic instrument identifies 17 Axis I DSM-III-R diagnoses, as well as ASPD, following a format similar to the Diagnostic Interview Schedule (DIS)⁵² and the Schedule for Affective Disorders and Schizophrenia (SADS).⁵³ As described elsewhere,⁴⁸ the SSAGA consists of 17 sections, the first three of which concentrate on demographics and medical history. The next four sections deal with tobacco, alcohol, marijuana and other drugs, with more detail on use patterns and problems collected for subjects who have used the relevant substance on multiple occasions. The subsequent sections cover most major mood, anxiety and psychotic disorders or ASPD, with each invoking a general screening question that allows subjects with no symptoms in that domain to skip to the next section. The interview has been demonstrated to have a high test-retest reliability, with a kappa of 0.84–0.90 for alcohol dependence and of 0.65–0.74 for life-time major depression, with kappas for most other major psychiatric diagnoses in the good to very good range.⁴⁸ An additional evaluation of the SSAGA revealed what 81–87% of the specific diagnostic items for dependence were in the fair or better ranges of reliability.⁴⁹

Several steps were taken to establish whether any diagnostic syndrome was likely to have occurred outside the context of substance use, medications or medical disorders (i.e. be independent).^{54,55} Using the approach developed by clinical researchers, in the initial step the interviewer established the age of onset of alcohol dependence, defined as the age of occurrence of the third of the nine DSM-III-R criterion items.⁴⁷ Then, all three-month or more periods of abstinence from alcohol or other relevant drugs were noted on the time-line. As described in another publication,⁴⁶ 70% of alcoholics have had such dry periods since the onset of alcohol dependence, spending between 20% and 25% of their alcoholic careers in an abstinent state. Thirdly, the ages of onset of all episodes for each major psychiatric syndrome were established. Finally, the time-line was evaluated by the interviewer, the supervising editor and, if necessary,

by a conference call that included clinical researchers to determine if the full psychiatric syndrome antedated the onset of alcohol dependence, or if the clinical syndrome developed or remained diagnostic after a period of at least 1 month of abstinence. If treatment for a substance use disorder or psychiatric syndrome had occurred, efforts were made to obtain and review clinical records. Thus, repeated efforts were made to identify a psychiatric condition that occurred outside the context of substance use disorder, if it existed. When a subject had both an independent and a concurrent disorder of the same type (e.g. panic disorder), only the independent category was used.

All interviewers were trained to use the SSAGA during a series of sessions. These involved between 3 and 8 weeks of studying the SSAGA, observing interviews, carrying out interviews with mock subjects, interviewing actual subjects under supervision and then independent interviewing. All completed interviews were reviewed by an editor at each site, and for some centers, by a clinician. Quality control of interviews and an assessment of "drift" of interviewing techniques were evaluated by occasional audio tapes of actual interviews which were shared across sites.

In the data that follow, the SSAGAs were evaluated for COGA Masterfile 44 for the 919 controls (including 468 women) and for the 2713 alcohol-dependent subjects (including 921 women). The alcoholic group was made up of 954 probands and 1759 alcohol-dependent relatives. The 2713 probands and their alcohol dependent relatives were placed into categories based on the occurrence of any of three major mood disorders (major depressive disorder, bipolar I disorder, or dysthymia), or the occurrence of any of four major anxiety disorders (panic disorder with or without agoraphobia, agoraphobia without panic, social phobia and obsessive-compulsive disorder). The same subjects were included for each disorder for which they met criteria. Reflecting initial concerns over reliability,^{6,61} clinical relevance, and difficulty interpreting results in a substance using population, the SSAGA did not include questions evaluating simple phobias, GAD, or post-traumatic stress disorder (PTSD), although a subsequent version developed in 1996 has begun to evaluate the latter two of these syndromes. All DSM-III-R diagnoses were evaluated using com-

Table 1. Life-time rates of three mood disorders in alcohol-dependent subjects and controls (%) by gender

Diagnostic group	Alcohol-dependent subjects (n = 2713)				
	Controls (n = 919)	Independent		Concurrent	Total
		Independent	Early onset		
<i>n</i> (%) Male	451 (49.1)				1792 (66.1)
Major depressive disorder					
Total	15.9	5.3	11.5 ^a	30.7	42.2 ^a
Male	9.3	3.1	8.3	30.1	38.4 ^a
Female	22.2	9.7	17.8 ^c	31.9	49.7 ^a
Bipolar disorder					
Total	1.0	1.1	2.3 ^c	1.5	3.8 ^a
Male	0.7	0.7	1.5	1.2	2.7 ^b
Female	1.3	1.9	3.7 ^b	2.2	5.9 ^a
Dysthymia					
Total	1.0	1.2	1.6	2.0	3.6 ^a
Male	0.2	0.6	1.0	1.2	2.2 ^b
Female	1.7	2.4	2.8	3.5	6.3 ^a
Any affective disorder					
Total	17.1	6.6	14.0 ^c	29.9	43.9 ^a
Male	9.8	3.9	9.9	29.7	39.7 ^a
Female	24.2	12.1	21.8	30.3	52.1 ^a

^a Comparison vs. controls significant at $p < 0.001$ or greater; ^b Comparison vs. controls significant at $p < 0.01$ or greater; ^c Comparison vs. controls significant at $p < 0.05$ or greater.

puter algorithms, and do not include best final labels that will be generated in some cases in the future through a systematic evaluation of all available information.

Pairwise comparisons presented in the tables and text were evaluated using χ^2 tests for categorical data, and as a Student's t -test for a comparison of continuous variables across groups.

Results

The control and alcohol-dependent groups had mean (\pm standard deviation) ages of 36.5 ± 14.3 and 38.7 ± 12.2 years ($t = -4.23$, $df = 1395.8$, $p < 0.001$). The racial distributions of controls and alcoholics were 84.7% vs. 74.7% Caucasian, 4.5% vs. 16.5% black, 5.9% vs. 6.0% Hispanic, 2.3% vs. 0.1% Asian and 2.7% vs. 2.7% other ($\chi^2 = 135.59$, $df = 4$, $p < 0.001$). Across the two groups 56.9% vs. 41.3% were married, 4.7% vs. 26.5% were divorced or separated and 38.3% vs. 30.5% had never been married ($\chi^2 = 221.05$, $df = 4$, $p < 0.001$). Among the 921 alcohol dependent women, the mean age of onset of alcoholism was 25.4 ± 9.4 years, with an onset of 24.4 ± 8.6 years for the alcohol-dependent men ($t = -3.93$, $df = 174$, $p < 0.0001$). For the alcohol-dependent group

the mean number of the 9 DSM-III-R alcohol dependent symptoms 6.1 ± 2.1 , and the maximum number of drinks per 24 hours in their life-time was 28.0 ± 21.2 .

Table 1 describes the life-time prevalence rates for three major mood disorders in the alcohol-dependent subjects and controls. The first data column displays the rates for controls for diagnoses that occurred outside the context, or appeared to be independent of medications, substances of abuse or physical disorders. Regarding the alcohol-dependent subjects, data in the second column relate to major mood disorders that occurred outside the context of a substance use disorder and prior to the onset of alcohol dependence (i.e. were early onset). The third data column gives the *total* proportion of individuals who met criteria for a disorder reported to have been outside the context of a substance use disorder or similar condition, but now also including subjects for whom the mood disorder developed after the onset of alcohol dependence but during a period of abstinence. The next column of Table 1 offers information regarding the proportion of individuals who met criteria for a major mood disorder, but for whom the disorder only appeared to have occurred during the active phase of a preexisting condition such as

Table 2. Life-time rates of four anxiety disorders in alcohol-dependent subjects and controls (%) by gender

Diagnostic group	Controls (n = 919)	Alcohol-dependent subjects (n = 2713)				
		Independent	Independent		Concurrent	Total
			Early onset	Total		
<i>n</i> (%) Male	451 (49.1)				1792 (66.1)	
Panic disorder						
Total	1.0	2.8 ^b	4.2 ^a	1.0	5.2 ^a	
Male	0.7	1.5	2.8 ^b	1.1	3.9 ^a	
Female	1.3	5.2	6.8 ^a	0.9	7.7 ^a	
Agoraphobia						
Total	0.9	1.2	1.6	1.6	3.2 ^a	
Male	0.4	0.9	1.1	1.3	2.4 ^b	
Female	1.3	1.9	2.6	2.2	4.8 ^a	
Social phobia						
Total	1.4	3.0 ^c	3.2 ^b	1.1	4.3 ^a	
Male	0.7	2.2	2.4 ^c	0.6	3.0 ^b	
Female	2.1	4.6	4.9 ^c	1.9	6.8 ^a	
Obsessive-compulsive disorder						
Total	0.9	1.3	1.3	1.2	2.5 ^a	
Male	1.0	1.0	1.0	1.5	2.5 ^c	
Female	0.6	1.9	1.9	0.5	2.5 ^c	
Any anxiety disorder						
Total	3.7	7.5	9.4 ^a	2.4	11.8 ^a	
Male	2.4	5.1	6.7 ^a	2.6	9.3 ^a	
Female	4.9	12.1	14.7 ^a	1.9	16.6 ^a	

^a Comparison vs. controls significant at $p < 0.001$ or greater; ^b Comparison vs. controls significant at $p < 0.01$ or greater; ^c Comparison vs. controls significant at $p < 0.05$ or greater.

alcohol dependence (i.e. a concurrent condition). The final column is the total proportion for each major mood disorder among alcohol-dependent subjects, and represents the sum of individuals with mood disorders reported outside or within the the context of substance use disorders. In Tables 1 and 2, data are offered separately for males in females, and also for the total population.

As presented at the bottom of Table 1, some independent major mood disorder was seen in 14.0% of the alcohol dependent subjects and in 17.1% of controls ($\chi^2 = 5.15$, $df = 1$, $p < 0.05$). Using the methods employed here, these overall figures regarding rates of independent major mood disorders did not indicate a significant increased risk for these syndromes among alcoholic men or women compared to controls. While the lack of impressive difference between alcoholics and controls for the overall rate of affective disorders makes more detailed comparisons by specific mood disorders tenuous, and raises the possibility of a Type 1 error, a visual inspection of Table 1 reveals some interesting

results. The alcoholic group did show a significantly higher life-time rate of independent bipolar disorder than controls ($\chi^2 = 5.85$, $df = 1$, $p < 0.05$), a result which was significant for women ($\chi^2 = 6.44$, $df = 1$, $p < 0.05$) but not for men. There were no significant differences between alcoholics and controls for independent dysthymic disorders, and the risk for independent major depressive disorders was actually slightly, but significantly lower in alcoholics than controls ($\chi^2 = 11.99$, $df = 1$, $p < 0.001$), a difference mostly accounted for by women ($\chi^2 = 3.89$, $df = 1$, $p < 0.05$).

A second finding in Table 1 is the high rate of concurrent major mood disorders among the alcoholic group. Almost 30% of alcohol dependent subjects had some form of an "induced" or concurrent major depressive episode in the context of a substance use or similar disorder, with rates for men resembling those for women. Thus, the 14% overall estimate for an independent mood disorder increased more than three-fold to a 44% rate for affective syndromes if concurrent disorders were considered. While not

as dramatic, the 2.3% rate for bipolar disorder relevant to independent disorders increased almost two-fold to 3.8% once concurrent disorders were added, and dysthymia increased over two-fold from 1.6% to a total of 3.6% when concurrent disorders were included in the total.

Table 2 uses the same general format as Table 1 to describe life-time rates for each of the four major anxiety disorders for alcoholics and controls. Here, 9.4% of the alcohol dependent subjects had at least one of the four independent major anxiety disorders, versus 3.7% among controls ($\chi^2 = 30.45$, $df = 1$, $p < 0.001$), including 6.7% of the male alcoholics versus 2.4% among controls ($\chi^2 = 11.88$, $df = 1$, $p < 0.001$), and 14.7% of the female alcoholics versus 4.9% among controls ($\chi^2 = 29.22$, $df = 1$, $p < 0.001$). To avoid Type 1 errors, the major emphasis of these analyses has been placed on these values for the combined total of the four anxiety disorders. However, interesting data are also offered regarding specific diagnoses. The clearest increased rates for independent anxiety disorders among alcoholics were seen for panic disorder (4.2% of the alcoholics had an independent panic disorder versus 1.0% of controls; $\chi^2 = 21.46$, $df = 1$, $p < 0.001$), with significantly higher rates compared to controls for both male ($\chi^2 = 7.05$, $df = 1$, $p < 0.001$) and female alcoholics ($\chi^2 = 20.31$, $df = 1$, $p < 0.001$). Substantial increased risks for independent disorders among alcoholics were also observed for social phobia (3.2% vs. 1.4%; $\chi^2 = 8.49$, $df = 1$, $p < 0.001$) with, once again, significant differences seen for alcoholics versus control men ($\chi^2 = 5.39$, $df = 1$, $p < 0.05$) and women ($\chi^2 = 6.17$, $df = 1$, $p < 0.05$). However, there was no significant increased risk for either agoraphobia or obsessive-compulsive disorder for alcoholics compared to controls.

Because anxiety disorders often have an onset before the age of 30, (Blazer, 1995; Fyer *et al.*, 1995; Barlow & Liebowitz, 1995; Jenike, 1995) the clearest case for independent major anxiety disorders can be made for those clinical conditions (given in the second data column) with an onset prior to alcohol dependence for this sample with an onset of alcoholism in the mid-twenties. However, even if this more conservative figure is used, the rates of independent panic disorder (2.8% vs. 1.0%; $\chi^2 = 9.68$, $df = 1$, $p < 0.01$), and of social phobia (3.0% vs. 1.4%; $\chi^2 = 5.29$, $df = 1$, $p < 0.05$) remained signi-

ficantly elevated among alcoholics compared to controls. These findings reflect the fact that 79.8% of the alcohol dependent subjects with an independent major anxiety disorder had an onset of their anxiety syndrome before the onset of alcohol dependence.

The proportion of alcoholics with any major anxiety disorder increased from 9.4% for independent disorders to 11.8% when concurrent conditions were considered. The latter was a 25.5% higher rate than for independent conditions alone, even in a study using diagnostic criteria with rigid demands for clinical relevance.

The data in Tables 1 and 2 were re-evaluated in light of several demographic characteristics that might have influenced the results. The information presented in these tables remained unchanged when, in an effort to avoid analyses of closely related subjects, probands were evaluated separately. Nor did the results change greatly when alcoholics with or without histories of alcoholic inpatient treatment were analyzed separately, or when only subjects old enough to have passed through most of the age of risk for most of the disorders (e.g. age 45 years or older) were considered. Of course, the two tables have already demonstrated that the same types of conclusions were apparent for the two genders.

Tables 3 and 4 explore one aspect of whether the distinction between concurrent and independent mood and anxiety disorders was appropriately executed. Because most major mood and anxiety disorders are familial and often genetically influenced,⁵⁶⁻⁶⁰ one would expect that the close relatives of individuals with an independent disorder would have higher rates of similar syndromes compared to relatives of individuals for whom the psychiatric syndrome was concurrent with and possibly induced by another condition. In order to avoid the complexities encountered when subjects are viewed from the perspective of their biological relationships to every other potential family member, these tables deal only with interviewed first-degree relatives of alcohol-dependent probands.

The second and third data columns of Table 3 reveal that independent major depressive disorders occurred in 22.1% of the interviewed first-degree relatives of 88 alcoholic probands with an independent major depression. This life-time risk was significantly higher than the 17.3% rate for 1,592 relatives of probands with concurrent depression ($\chi^2 = 4.21$, $df = 1$, $p < 0.05$), and

Table 3. *Life-time rates of three major mood disorders in interviewed first-degree relatives of alcohol-dependent probands by proband's mood diagnosis group (%)*

First-degree relative's independent mood disorders	Proband's mood disorder diagnoses										
	Major depressive disorder			Bipolar disorder			Dysthymia			Any mood disorder	
	None	Independent	Concurrent	Independent	Concurrent	Independent	Concurrent	Independent	Concurrent	Independent	Concurrent
N probands	449	88	399	27	24	13	26	115	390	115	390
N first-degree relatives	1702	335	1592	114	100	51	128	459	1545	459	1545
Major depressive disorders	14.6	22.1 ^{a,d}	17.3 ^c					21.4	17.5		
Bipolar disorder	1.1			3.5 ^c	1.0		3.3	0.9			
Dysthymia	1.1					3.9	2.3	1.5			
Any independent mood disorder								23.8 ^a	19.0 ^{c,f}		

^a Comparison vs. the Column 1 no diagnosis group $p < 0.001$; ^b Comparison vs. the Column 1 no diagnosis group $p < 0.01$; ^c Comparison vs. the Column 1 no diagnosis group $p < 0.05$; ^d Comparison of Independent vs. Induced diagnostic groups $p < 0.001$; ^e Comparison of Independent vs. Induced diagnostic groups $p < 0.01$; ^f Comparison of Independent vs. Induced diagnostic groups $p < 0.05$.

Table 4. Life-time rates of four major anxiety disorders in interview first-degree relatives of alcohol-dependent probands by proband's mood diagnosis group (%)

First-degree relative's independent mood disorders	Proband's mood disorder diagnoses														
	None			Panic disorder			Agoraphobia			Social phobia			Obsessive-compulsive disorder		
	None	Independent	Concurrent	Independent	Concurrent	Concurrent	Independent	Concurrent	Concurrent	Independent	Concurrent	Concurrent	Independent	Concurrent	
N probands	822	44	18	13	22	30	16	20	17	94	38				
N first-degree relatives	3185	176	83	41	88	113	70	85	58	365	156				
Panic disorder	3.2	9.1 ^{a,f}	1.2							5.2	3.2				
Agoraphobia	1.4			2.4	3.4					1.9	0.0				
Social phobia	2.1					6.2 ^b	2.9			3.6	1.9				
Obsessive-compulsive disorder	1.0							1.2	0.0	1.1	0.0				
Any independent	6.8									10.7 ^{b,f}	5.1				

^a Comparison vs. the Column 1 no diagnosis group $p < 0.001$; ^b Comparison vs. the Column 1 no diagnosis group $p < 0.01$; ^c Comparison vs. the Column 1 no diagnosis group $p < 0.05$; ^d Comparison of Independent vs. Induced diagnostic groups $p < 0.001$; ^e Comparison of Independent vs. Induced diagnostic groups $p < 0.01$; ^f Comparison of Independent vs. Induced diagnostic groups $p < 0.05$.

higher than the 14.6% rate of this disorder in the 1702 relatives of the 449 probands with no history of an independent or concurrent mood disorder ($\chi^2 = 11.67$, $df = 1$, $p < 0.001$). Similarly, for bipolar disorder 3.5% of the 114 interviewed first-degree relatives of probands with independent manic episodes had at least one bipolar disorder episode, a rate significantly higher than the 1.1% rate in relatives of probands with no affective disorder ($\chi^2 = 4.89$, $df = 1$, $p < 0.05$), although not significantly more than the 1.0% risk for relatives of alcoholics with concurrent manias ($\chi^2 = 1.47$, $df = 1$, $p < 0.23$). While, perhaps, reflecting the relatively low rates of these disorders, the numbers were not statistically significantly different, similar trends were noted regarding relatives of alcoholic probands with independent and concurrent dysthymias.

The results in Table 4 regarding anxiety disorders are similar to those in Table 3. Panic disorder was observed during the life-time of 9.1% of the 176 interviewed first-degree relatives of the 44 probands who, themselves, had an independent panic disorder. This rate was significantly higher than the 3.2% rate among the 3185 relatives of the 822 probands who qualified for no independent or concurrent anxiety disorder ($\chi^2 = 17.39$, $df = 1$, $p < 0.001$). It was also higher than the 1.2% rate among the 83 relatives of 18 alcoholics with concurrent panic ($\chi^2 = 5.72$, $df = 1$, $p < 0.05$). Similar conclusions applied to social phobia, with rates of 6.2% in the 113 relatives of the probands with independent social phobia, a figure that was higher than the 2.1% among the 3185 relatives of the probands with no anxiety disorder ($\chi^2 = 8.33$, $df = 1$, $p < 0.01$), and higher than the 2.9% in the 70 relatives of the alcoholic probands with induced social phobia ($\chi^2 = 1.03$, $df = 1$, $p < 0.31$). There were no significant differences regarding the relatives of probands with independent versus induced agoraphobia or obsessive-compulsive disorders. These two latter diagnoses, however, did not demonstrate any significant differences between alcoholics and controls in Table 1.

Discussion

These data from a large sample of subjects indicate that 90% of the alcohol-dependent men and women did not demonstrate any of the four independent major anxiety disorders, and 86%

of the sample had no evidence of any of the three independent major mood disorders. The study found no evidence that in this sample alcoholism was associated with an increased risk for independent major depressive disorder, obsessive-compulsive disorder or agoraphobia. This same methodology, however, indicated that these alcohol-dependent subjects had a two-fold increased risk for manic depressive disease, and three-fold or higher increased risk for panic disorder and social phobia.

These results complement the data reported from large epidemiological surveys^{2,3,5} and several evaluations of alcohol-dependent men and women entering treatment.^{6,18,14} The present study incorporates methodology aimed at distinguishing between anxiety and depressive disorders that began either before the onset of alcohol dependence or remained during the 3-month or more periods of abstinence observed in two-thirds or more of alcoholic individuals after the onset of alcoholism.⁴⁶ These independent disorders were distinguished from depressive or anxiety states which were only retrospectively reported to have occurred concurrent with periods of heavy drinking or related conditions, a situation in which the prognosis and treatments might be different from independent affective and anxiety states.^{29-31,38,39}

However, it is possible that the rate of independent disorders reported here might represent the lower end of the range of such conditions. It is important to remember that no data were available on GAD or PTSD. Also the data reveal a slight, but significant, lower rate of independent major depressive episodes for the alcohol dependent subjects than controls. At the same time because of the emphasis on alcohol dependence, not potentially injudicious drinking, it is possible that some of the seemingly independent mood and anxiety conditions might have really been substance-induced at levels of alcohol intake that were substantial, but predated the onset of definite dependence. Thus, it is likely that the true rate of independent disorders among alcoholics rests somewhere between the figures reported by the three types of investigations including epidemiological surveys, evaluations of populations entering treatment and studies such as this gathering detailed chronological information from a large number of alcoholic individuals from diverse settings.

There are a number of methodological issues

that might have contributed to the range of psychiatric disorders observed across studies. The COGA evaluations begin with the identification of alcohol-dependent subjects who were selected because of a relatively dense family history of alcoholism. This step, along with the emphasis on probands undergoing inpatient treatment for alcoholism, might have decreased the opportunity to identify alcoholic individuals whose diagnoses were more closely related to other psychiatric conditions. A second methodological problem, one inherent in all three types of investigations, is the retrospective nature of the data collection procedures where reports on the life-time prevalence of various disorders are subject to the vagaries of memory and the veracity of the subjects. However, the SSAGA has been demonstrated to have relatively good levels of reliability when tested both within and across research centers.^{48,49} Other structured diagnostic instruments, such as the DIS, have kappa statistics ranging from 0.3 to 0.4 for panic disorder, major depressive disorder and social phobia, to 0.8 or higher for many of the substance use disorders and ASPD.⁶¹ Nonetheless, only a prospective investigation where diagnostic information is routinely obtained from multiple informants is likely to yield the most accurate results.

A third methodological difficulty, one that can only be overcome if highly sensitive and specific biological tests are developed to distinguish between major psychiatric disorders, is a consequence of the emphasis on gathering a history of the chronology of development of psychiatric syndromes in the present analyses. Thus, it is possible that some alcohol-dependent men and women developed an independent mood or anxiety disorder while drinking heavily, using drugs of abuse, or in the context of a similar condition. This would be especially problematical for the one-third or so of alcoholics for whom no long-term period of sobriety had been documented.⁴⁶ However, several research groups have presented evidence that, despite the errors inherent in a time-line based diagnostic approach, the large majority of individuals who were noted to have concurrent or substance-induced disorders demonstrated a rapid improvement in their psychiatric conditions. In many ways these alcoholics ran a clinical course more consistent with alcohol dependence than with an independent psychiatric disorder.^{30-32,38}

Additional support for the overall accuracy of

the "independent versus concurrent" distinction comes from the evaluation of the rate of psychiatric disorders in the families in the present and other reports.^{25,47} Thus, those subjects with independent major depressive disorder, manic depressive disease, social phobia and agoraphobia had significantly higher rates of similar independent psychiatric disorders among their first-degree relatives than did controls. These subjects also demonstrated a consistent trend in the same direction regarding higher rates of such disorders in first-degree relatives compared to those relatives with concurrent disorders. At the same time, Table 3 offers some indication of heterogeneity remaining within the sample labeled as having a concurrent depressive episode, as the rate of independent depressions in the relatives of these subjects was slightly, but significantly, higher than the rate reported for control individuals.

The strength of the availability of data from interviewed relatives of alcohol dependent probands also creates a potential problem. The data in Tables 1 and 2 include information from multiple alcohol dependent people from the same pedigree. Thus, it is important that the major findings were reestablished when only probands were evaluated, with similar results. Nor did the major findings differ when only alcoholics with histories of inpatient treatment were considered. Nonetheless, because of the manner in which probands and their families were chosen, it is important to recognize that the generalizability of the present results has not been fully established.

A fifth methodological consideration relates to the difficulty in establishing an appropriate control group in this type of investigation. Indeed, one of the major strengths of the national epidemiological studies is that a single large population was selected at random (within predefined parameters), with the resulting comparisons between those with and without a disorder not requiring any additional control groups. Thus, even though the same interview and interpretative techniques were used for controls, original probands, and their relatives in the present investigation, the true differential rate in life-time psychiatric disorders between alcoholics and controls must be interpreted with caution.

Despite these caveats, as well as the need to interpret these results as only one of many possible ways to study the question, there are a

number of potential implications of this work. There is agreement between all three types of approaches (epidemiological, evaluations of treatment samples and the present hybrid approach) that there are likely to be elevated rates of alcohol dependence among individuals with manic depressive disease, ASPD, panic disorder and social phobia. Because heavy doses of alcohol are likely to intensify the symptoms of any pre-existing psychiatric disorders,^{19,62} clinicians should make extra efforts to screen for alcohol dependence among these patients. Educational programs aimed at increasing awareness of the problems associated with alcoholism and the need to be on guard against the development of repetitive alcohol problems should be considered for men and women with these pre-existing psychiatric disorders. These findings also corroborate the need for additional research to evaluate the possible genetic linkage between alcohol dependence and these psychiatric disorders, and to explore other ways in which one diagnosis increases the probability of developing the other.

A second implication is that both the present study and the ECA investigation^{1,2} indicate that the majority of alcohol dependent men and women do not have any of the major anxiety or mood disorders investigated here. The significantly higher rate of psychiatric syndromes reported in the NCS study overall, as well as the elevated risk for these psychiatric syndromes among alcoholics, require further investigation.^{3,4} Differences between studies probably reflect approaches to the training and supervision of interviewers, the methods used to screen for psychiatric disorders, as well as the threshold used for the diagnosing syndromes such as social phobia.^{63,64} Thus, at least two of the types of investigations cast doubt on the supposition that the majority of alcohol-dependent men and women developed their disorder in the context of a pre-existing major anxiety or depressive syndrome. These data are also consistent with the prospective studies of children of alcoholics which demonstrate a high risk for alcohol dependence, but little evidence of pre-existing major mood or anxiety disorders in the large majority of these young men and women who went on to develop alcoholism.⁶⁵⁻⁶⁷ Similarly, studies of individuals who have had an early onset of a major mood disorder did not document increased risks for the later develop-

ment of alcohol dependence.^{68,69} Nonetheless, additional prospective studies of people at high risk for other major psychiatric disorders, as well as investigations of those with early onset major psychiatric syndromes will be required before the true level of risk for subsequent alcohol dependence can be established.

Thirdly, the substantial proportion of alcohol dependent men and women who reported having developed mood and anxiety syndromes in the context of heavy drinking or withdrawal has some potential implications regarding treatment. Even for those mood and anxiety disorders that dissipate over a period of 4-6 weeks of abstinence,^{30,38} it is important to determine whether specific behavioral, cognitive or pharmacological approaches might increase the rate of disappearance of the psychiatric symptoms, or decrease the risk for returning to heavy drinking. Establishing a distinction between concurrent (or, as DSM-IV labels them, induced) disorders and psychiatric conditions that appear to have developed independently of periods of heavy drinking might reveal some treatment approaches that have had a substantial impact on only one of these two important subgroups. Thus, evaluations of anti-anxiety medications such as buspirone have generated mixed results in different studies,^{70,71} a phenomenon which might be explained by differing proportions of subjects with concurrent and independent anxiety conditions. Similarly, while the majority of investigations of lithium, tricyclic-type antidepressants and selective serotonin reuptake inhibitors (SSRI) have revealed little evidence that these medications help with levels of depression or decrease the chances of returning to drinking,^{35,72-76} several small scale and short-term studies have indicated potential promise.^{77,78} The most recent of these investigations⁷⁷ prescribed flexible doses of desipramine to 15 alcoholics who remained depressed after at least 1 week of abstinence, reporting significantly lower levels of depression and longer periods of abstinence associated with the active drug compared to a placebo group. Here again the divergence in results between investigations might reflect, in part, heterogeneity of the treated samples, especially with regard to issues related to concurrent versus independent depressive disorders.

In conclusion, the relationship between alcohol dependence on one hand, and major

mood or anxiety disorders, on the otherhand, is complex. Like the proverbial elephant being evaluated by a cadre of blindfolded observers, the optimally informative picture might depend upon efforts to describe the subject from a variety of perspectives, none of which is capable of assimilating the entire picture. From that viewpoint, the methods inherent in the COGA investigation might add another relevant approach to this difficult but clinically relevant topic.

Acknowledgements

The Collaborative Study on the Genetics of Alcoholism (COGA) (H. Begleiter, SUNY HSCB Principal Investigator, T. Reich, Washington University, Co-Principal Investigator) includes six different centers where data collection takes place. The six sites and Principal Investigator and Co-Investigators are: Indiana University (J. Nurberge Jr, T.-K. Li, P. M. Conneally, H. Edenberg); University of Iowa (R. Crowe, S. Kuperman); University of California at San Diego and Scripps Institute (M. Schuckit, F. Bloom); University of Connecticut (V. Hesselbrock); State University of New York, Health Sciences Center at Brooklyn (H. Begleiter, B. Porjesz); Washington University in St Louis (T. Reich, C. R. Cloninger, J. Rice). This national collaborative study is supported by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) by USPHS grants NIAAA U10AA08403.

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