
Special Article

Alcohol Dependence and Anxiety Disorders: What Is the Relationship?

Marc A. Schuckit, M.D., and Victor Hesselbrock, Ph.D.

***Objective:** In this critical review the authors evaluate the literature regarding the relationship between lifelong DSM-III-R anxiety disorders and alcohol dependence. Many alcohol-dependent individuals demonstrate severe anxiety symptoms in the context of acute or protracted abstinence syndromes, but it is unclear whether these anxiety conditions are independent psychiatric disorders or temporary syndromes likely to disappear on their own. **Method:** Reports since 1975 describing the relationship between alcoholism and anxiety disorders were reviewed to determine whether 1) lifelong anxiety disorders are unusually prevalent among alcohol-dependent individuals, 2) children of alcoholics are more likely to develop anxiety disorders than comparison populations, 3) anxiety syndromes are likely to disappear with abstinence, 4) the rate of alcohol dependence among subjects with lifelong anxiety disorders is higher than normal, 5) there is familial crossover between alcohol dependence and anxiety disorders, and 6) alcoholism is often preceded by anxiety disorders in groups from the general population studied prospectively. **Results:** The interaction between alcohol use and anxiety disorders is complex. The available data, while imperfect, do not prove a close relationship between lifelong anxiety disorders and alcohol dependence. Further, prospective studies of children of alcoholics and individuals from the general population do not indicate a high rate of anxiety disorders preceding alcohol dependence. **Conclusions:** The high rates of comorbidity in some studies likely reflect a mixture of true anxiety disorders among alcoholics at a rate equal to or slightly higher than that for the general population, along with temporary, but at times severe, substance-induced anxiety syndromes.*

(Am J Psychiatry 1994; 151:1723-1734)

Two out of every three "alcoholics" meet criteria for another major psychiatric disorder at some time in their lives (1-4). The majority of these additional diagnoses relate to antisocial personality disorder

and other drug dependencies, but the rates of depressive and anxiety syndromes also appear to be higher than expected by chance alone (5-7). While few would disagree with the conclusion that there is an interaction between alcohol-related life problems and symptoms of anxiety or depression, there is a vigorous debate regarding the implications of the association.

All severe depressions or anxiety states must be clinically recognized and treated appropriately (8). However, at least one major school of thought insists that to achieve the optimal impact of any intervention, the clinician and researcher must also seek to determine whether there are important subgroups of individuals with similar mood or affective clinical pictures (9). The goal is to identify additional characteristics that indi-

Presented at the 146th annual meeting of the American Psychiatric Association, May 22-27, 1993, San Francisco. Received July 30, 1993; revisions received March 29 and May 16, 1994; accepted June 15, 1994. From the Department of Psychiatry, School of Medicine, University of California, San Diego, and the Department of Psychiatry, VA Medical Center, San Diego. Address reprint requests to Dr. Schuckit, Department of Psychiatry (116A), VA Medical Center, 3350 La Jolla Village Dr., San Diego, CA 92161-9116.

Supported by grants AA-05226, AA-08401, AA-08403, and AA-03510 from the National Institute on Alcohol Abuse and Alcoholism and by the Veterans Affairs Research Service.

cate that the prognoses and treatments for some anxiety or depressive states might be substantially different from one another (5, 8). For example, depressive syndromes that are observed only in the context of some medical conditions (e.g., thyroid disorders) or drug treatments (e.g., antihypertensive therapy) require all of the emergency steps relevant for any severe depression. However, the prognoses for these "organic" mood disorders include a high likelihood that the affective symptoms will disappear with time alone after appropriate treatment of the hormonal condition or an adjustment of the blood pressure medication (10). Similarly, as has been discussed elsewhere, major depressive episodes observed only in the context of intoxication or withdrawal from substances of abuse are likely to clear spontaneously over time following abstinence, and there is little indication that they routinely require antidepressant medications (5, 11).

Similar to the data regarding affective disorders, the literature also indicates a high prevalence of anxiety symptoms among alcohol-dependent individuals (8, 12). Some clinicians and researchers have taken these data to indicate that anxiety and alcohol use disorders might be genetically linked. Others have concluded that many individuals with major anxiety disorders might be attempting to medicate their symptoms with alcohol (13). However, it is not clear from the existing literature whether the high rate of anxiety problems appearing only in the context of heavy drinking or withdrawal indicates the existence of lifelong anxiety disorders that will require long-term treatment. It is possible that the majority of these situations involve temporary anxiety symptoms observed only during intoxication and withdrawal.

GENERAL FACTORS THAT COMPLICATE DATA INTERPRETATION

Several overarching factors complicate the interpretation of the data accumulated to date regarding the relationship between anxiety symptoms and alcohol use disorders. First, documenting symptoms is not equivalent to establishing a diagnosis. A number of studies have shown that the correspondence between cases identified by means of a symptom checklist and a clinical diagnosis is far from perfect. In fact, in one study the sensitivity of these measures for identifying a DSM-III-R lifetime diagnosis of depression was less than 75%, and the specificity was less than 55% (1). Similarly, the specificity of the Michigan Alcohol Screening Test (MAST) (14) for identifying cases of true alcoholism may be as low as 36% (15). Differences in symptoms surveyed, determining whether symptoms cluster, and assessing the severity of the symptoms are likely causes of the discrepancy between cases identified by a symptom checklist and those receiving a clinical diagnosis.

In this context, acute or protracted withdrawal from alcohol is characterized by a high rate of anxiety symptoms (16–19). In several studies 80% of alcohol-de-

pendent men admitted to ever having repetitive panic attacks in the course of withdrawal from alcohol, and 50%–67% of the alcohol-dependent men had high scores on state anxiety measures, with symptoms that resembled generalized anxiety disorder and social phobia (16). If seen only in the context of withdrawal, these and other symptoms are likely to disappear with time (20–29). Thus, when phobic, panic-like, or other anxiety pictures are observed during acute or protracted withdrawal, it is difficult to determine from a cross-sectional evaluation whether the individual has a major anxiety disorder, with the implied lifelong course of anxiety symptoms (30), or whether these symptoms are likely to disappear with time.

A related issue involves differences between studies in the criteria used for "alcoholism." Some authors discuss alcohol-related "problems," others focus on alcohol abuse, and still others consider dependence. In addition, the criteria for alcoholism, alcohol abuse, and alcohol dependence have changed over the last few decades (9, 10, 15).

A second factor that jeopardizes interpretation of the rates of anxiety disorders among alcoholics is assortative mating (31). Most individuals do not select a mate by chance alone; rather, they tend to choose someone on the basis of their physical characteristics, ethnic background, etc. (32). An important factor in mate selection appears to be the probability that an individual with a major behavioral or psychiatric syndrome is more likely than others from the population to select a mate with problems. In one study (33) two-thirds of individuals with a major depressive disorder selected a spouse with a psychiatric syndrome, while other publications suggest that alcohol-dependent individuals are likelier than average to select a spouse with alcohol, drug, severe antisocial, or psychiatric problems (34–37). Additional studies indicate that alcohol-dependent individuals with major depression or other psychiatric syndromes are more likely than nondepressed alcoholics to have a parent with that second disorder (5, 38, 39). Once assortative mating is considered, the rate of anxiety disorders in relatives of alcoholics decreases by about 10% (40). Thus, the finding of a bona fide major anxiety disorder among alcohol-dependent individuals could be the result of a family history of major anxiety disorders independent of their own drinking problems.

A third complication occurs when subjects are asked for their opinion about whether the alcohol or anxiety syndrome came first. Such queries usually involve the unstructured solicitation of opinions from subjects; few studies have required careful documentation of data and generation of information from additional informants. A number of investigators have reported that when alcohol and anxiety disorders are seen in the same individual, 40%–60% of subjects indicate that the anxiety disorder appeared first (1, 41–44). However, when more vigorous approaches are used, subjective opinions are likely to be found to be inaccurate. Stockwell and Bolderston (20) pointed out that the subject is likely to name the first symptom of nervousness he or

she ever experienced, not a full-blown diagnosable disorder. At least two groups of investigators (45, 46) have followed up on self-reports by gathering data from additional informants or reviewing earlier case records. Those studies showed that for two-thirds of the patients who felt that the alcohol problems developed later than the behavioral condition, there was evidence of severe alcohol-related life problems *before* other diagnosable anxiety syndromes were observed. This finding is also supported by a 40-year follow-up of college freshmen that revealed no evidence of antecedent anxiety disorders in alcoholics (47, 48), by evaluations of anxiety in identical twins of alcoholics that revealed anxiety disorders only subsequent to alcoholism (49), and by a prospective evaluation of a general community sample (21). Thus, even though in some investigations efforts were made to determine whether the anxiety syndromes appeared independently of the heavy drinking, more vigorous studies indicate that in at least two-thirds of the individuals who seem to have both psychiatric and alcohol-related disorders, it is the alcohol-related syndromes that appeared first.

Fourth, few studies of the relationship between alcohol and anxiety disorders controlled for the possibility that both the alcohol and anxiety conditions might be related to a third diagnosis, such as another drug dependence syndrome, especially one involving stimulants. Comorbid drug use and associated disorders can be seen in many alcohol-dependent men and women and are observed at high rates among people with antisocial personality disorder, two-thirds of whom develop severe life problems with both alcohol and drugs (50, 51). The subsequent intoxication with stimulant drugs, such as amphetamines and cocaine, can cause intense feelings of anxiety, panic attacks, phobic-type behavior, and even obsessional behavior (10). Thus, even documentation that an alcohol-dependent individual at some point in his or her life demonstrated panic attacks severe enough to fulfill criteria for panic disorder tells the researcher and clinician little about the probable future course and optimal long-term treatment if these anxiety symptoms were observed only in the context of severe intoxication with stimulants. The same is true for almost any anxiety syndrome seen in this context.

Of course, additional factors can affect the levels of anxiety symptoms observed in alcohol-dependent individuals. Most men and women come to treatment in the context of severe life problems, conditions that can themselves add to symptoms of anxiety. In addition, many alcohol-dependent men and women have grown up in homes that lack a stable environment, often reflecting the impairments that accompany alcohol use disorders, drug use disorders, and antisocial personality disorder, which are frequently seen in the parents of alcohol-dependent individuals (52). This level of life stress and problems with adjustment to difficulties during early periods of development can themselves add severe anxiety symptoms that might not represent independent anxiety disorders (53, 54). Also, many of these

alcoholic subjects might be demonstrating anxiety symptoms that relate to organic deficits, including a fetal alcohol effect (55). Finally, because of the demanding nature of work on comorbid syndromes, many of the studies involved a limited number of subjects. Unfortunately, small sample sizes have relatively low statistical power for detecting true relationships between variables. Estimates obtained from small samples are typically unreliable since they may either under- or overestimate the magnitude of the true relationship.

These considerations do not prove that alcohol-dependent men and women lack a high risk for lifelong anxiety syndromes. Nor do these complicating factors indicate that the clinician should ignore anxiety syndromes when they occur. All such patients require careful evaluations and reassurance, and many can benefit from behavioral interventions that can decrease the intensity of symptoms. However, the complications noted here make it difficult 1) to draw definitive conclusions regarding whether alcohol-dependent men and women are more likely than the general population to demonstrate severe major anxiety syndromes requiring long-term treatment and 2) to determine whether alcohol and anxiety disorders are linked.

Recognizing the problems in interpreting the literature without carefully evaluating the methods involved, we examined six types of data related to the relationship between alcohol dependence and major anxiety disorders. Even after these evaluations, methodological problems remain that jeopardize conclusions. These remaining caveats include an absence of appropriate comparison subjects and imprecise and changing definitions of alcoholism and anxiety syndromes. However, the studies are clear enough to raise the question of whether there is a close relationship between alcoholism and lifelong anxiety disorders in the majority of patients.

METHOD

The methods used in this critical review of the literature began with a MEDLINE search of all English-language articles published in refereed journals since 1975 and presenting original data on the relationship between alcoholism and major anxiety disorders. All such articles were reviewed and formed the basis for the information presented here.

We approached the data in several ways. First, we critically reviewed the existing literature on the rate of anxiety disorders among alcohol-dependent individuals, considering as many of the methodological complexities outlined in the preceding section as possible. The adjusted rates were based on the proportion of subjects reported to have an anxiety syndrome that developed before the alcoholism. In the absence of such estimates within the study, an overall estimate was used, as will be explained. Then the overall mean rate was developed by determining the number of subjects in each study likely to have had an anxiety syndrome independent of alcoholism; these numbers were added across all studies, and that number was divided by the total number of subjects. When an adjusted rate involved a range, the average rate was used. For example, for a range of 10% to 20% the overall adjusted figure of 15% was used in computing the overall mean.

In the second type of evaluation, in an effort to overcome many of the caveats outlined in the preceding section, the rate of anxiety dis-

TABLE 1. Studies of Panic Disorder Among Alcoholics^a

Study	Number of Alcoholic Subjects	Stage of Alcoholism Treatment	Panic Disorder		
			Total Rate (%)	Panic Disorder Preceded Alcoholism (%)	Adjusted Rate (%) ^b
Block et al. (unpublished, 1990)	95	After 1 week of abstinence	25	40	10
Bowen et al. (56)	48	After 5-7 days of abstinence	21	—	5-10
Chambless et al. (57)	75	After detoxification	9	80	7
Cox et al. (58)	144	After 1 week of abstinence	33	—	8-17
Hesselbrock et al. (1)	321	—	6	56	3
Norton et al. (41)	102	First phase of treatment	28	40	11
Nunes et al. (59)	25	Within days of admission	60	—	—
Powell et al. (60)	565	After detoxification	13	—	3-7
Ross et al. (42)	370	—	11	58	6
Weiss and Rosenberg (43)	84	After detoxification	3	60	2
Overall	1,829	—	—	—	6 ^c

^aGeneral population lifetime rates: Kushner et al. (7): 1%; Regier et al. (4): 2%; Robins et al. (61): 1% overall, 1% for males; Robins et al. (62): 2%; Kessler et al. (63): 4% overall, 2% for males.

^bPossibly independent of the temporary effects of alcohol.

^cMean value.

orders in children of alcohol-dependent individuals was analyzed. This evaluation was based on the premise that if alcohol dependence and anxiety disorders are closely tied together, the children of alcohol-dependent parents, themselves at high risk for the future development of alcoholism, should demonstrate a high rate of anxiety disorders. Third, prospective studies of alcohol-dependent individuals were evaluated for evidence of the development of a major anxiety disorder subsequent to the achievement of abstinence. Fourth, the rate of alcoholism among patients with anxiety disorders was determined. Fifth, the familial crossover between anxiety disorders and alcoholism was assessed. Finally, data from prospective studies in the general population were critically evaluated to determine whether there is evidence of a higher than normal risk for anxiety disorders in individuals who later go on to develop alcoholism.

RESULTS

Anxiety Disorders Among Alcohol-Dependent Individuals

The prominent articles in the literature dealing with the rate of anxiety disorders in alcoholic individuals are outlined in tables 1-5. In each table the third column contains the period of abstinence that preceded the evaluation of the subject. This information is important since high levels of anxiety and potential misdiagnoses of lifelong anxiety disorders are likely to occur during the first 2 weeks of abstinence because of the acute withdrawal or abstinence syndrome (66). These symptoms are likely to continue at a decreasing level of intensity over the subsequent months as part of protracted withdrawal (17). Unfortunately, as would be true in any critical literature review, there are differences in the criteria used for alcohol and anxiety disorders and most reports do not give separate figures for men and women. Also, few of these studies used a time line to indicate the actual development of diagnosable syndromes, and almost none incorporated information taken from a resource person. Thus, the results of these evaluations are not definitive, but trends can be observed.

The final column in each table offers a gross adjusted rate for anxiety disorder, usually relating to lifetime diagnoses, that might begin to exclude temporary organic conditions. This is also a rough estimate since so few studies controlled for the complicating factors we have outlined. Regarding the final column, if the authors themselves indicated the proportion of anxiety disorders that might have developed before the alcohol dependence/abuse, a prerequisite for having caused the substance use disorder, this number was multiplied by the rate of illness reported, to give an adjusted rate. It is important to remember that for the reasons already described, this is likely to be a substantial overestimate of the proportion of individuals who truly had anxiety disorders independent of their heavy drinking (20). When the authors did not estimate the rate of independent anxiety syndromes, an adjusted range of rates between 25% and 50% for independent disorders was selected on the basis of the overall average of estimated independent syndromes. The last row of each table offers the total number of subjects involved across all studies and the mean adjusted rate of anxiety disorder. A footnote to each table contains estimated lifetime rates for the relevant disorder in the general population from a series of reports (4, 7, 61-63).

The optimal table would offer data separately by gender and would indicate the level of methodological rigor involved in each study. Unfortunately, this would have made the tables so complex that interpretation would have been difficult. Thus, the reader is urged to return to specific references to estimate the level of confidence one can have in the results.

Table 1 summarizes 10 studies in which the rate of panic disorder (or at least repetitive panic attacks) among alcoholics was evaluated. Unfortunately, as is true of the studies in all the tables, various definitions of panic and alcohol-related disorders were used in different studies. The unadjusted rates for panic conditions ranged from 3% to 60%, and the adjusted figures ranged from 2% to 17%. The adjusted figures do not

TABLE 2. Studies of Agoraphobia Among Alcoholics^a

Study	Number of Alcoholic Subjects	Stage of Alcoholism Treatment	Agoraphobia		
			Total Rate (%)	Agoraphobia Preceded Alcoholism (%)	Adjusted Rate (%) ^b
Bowen et al. (56)	48	After 5-7 days of abstinence	12	—	3-6
Chambless et al. (57)	75	After detoxification	8	80	6
Hesselbrock et al. (1)	321	—	15	71	11
Mullancy and Trippett (64)	102	After 10 days of abstinence	17	—	4-9
Smail et al. (65)	60	After 2 weeks of abstinence	41	—	10-21
Stravynski et al. (44)	96	After 2 weeks of abstinence	9	64	6
Weiss and Rosenberg (43)	84	After detoxification	2	60	1
Overall	786	—	—	—	9 ^c

^aGeneral population lifetime rates: Kushner et al. (7): 6%; Regier et al. (4): 5%; Kessler et al. (63): 5% overall, 4% for males.

^bPossibly independent of the temporary effects of alcohol.

^cMean value.

TABLE 3. Studies of Obsessive-Compulsive Disorder Among Alcoholics^a

Study	Number of Alcoholic Subjects	Stage of Alcoholism Treatment	Obsessive-Compulsive Disorder		
			Total Rate (%)	Obsessive-Compulsive Disorder Preceded Alcoholism (%)	Adjusted Rate (%) ^b
Chambless et al. (57)	75	After detoxification	3	80	2
Hesselbrock et al. (1)	321	—	5	38	2
Powell et al. (60)	565	After detoxification	12	—	3-6
Ross et al. (42)	370	—	10	46	5
Overall	1,331	—	—	—	4 ^c

^aGeneral population rates: Kushner et al. (7): 3%; Regier et al. (4): 3%; Robins et al. (61): 3% overall, 2% for males; Robins et al. (62): 3%.

^bPossibly independent of the temporary effects of alcohol.

^cMean value.

take into account the confounding factors we have described. The adjusted, but still exaggerated, rates can be summarized as a mean of 6%, a figure that is somewhat higher than the general population lifetime rate for panic disorder but considerably lower than the estimates based on the raw data alone.

Table 2 outlines seven studies, incorporating 786 subjects, regarding the potential rate of agoraphobia among alcoholics. The unadjusted rates were 2%–41%, and the grossly adjusted rates were 1%–21%. These translate to an overall mean of 9%, a rate that is a bit higher than that in the general population (5% to 6% overall). Table 3, relating to obsessive-compulsive disorder, displays adjusted rates from 2% to 6%, with an overall mean similar to general population rates. Table 4 summarizes reports in the literature of social phobia among alcoholics; the grossly adjusted rates range from 1% to 20% (mean=9%). While higher than several of the general population rates reported, these figures are still inflated by all of the uncontrolled factors we have listed. Table 5 relates to generalized anxiety disorder. While the overall mean is skewed by the large number of people in one study, the median of 9% (the middle of the rates across studies) is similar to general population rates.

While this is a critical review of the literature and not a meta-analysis, the studies reflected in tables 1–5 indicate the possibility that, after additional factors are controlled for as much as possible, alcoholics report rates

of panic disorder and perhaps generalized anxiety disorder and social phobia that are higher than the rates for the general population, although the rates of other anxiety disorders do not appear to be higher than normal. However, even here, the adjusted (but still potentially inflated) rates for other anxiety disorders are only slightly in excess of those found in the general population. More studies using more rigorous approaches for diagnoses and incorporating appropriate comparison subjects are needed.

Anxiety Disorders Among Children of Alcoholics

Alcoholism is a genetically influenced disorder, and the risk for severe repetitive problems with alcohol (i.e., alcohol abuse or dependence) has been found to be three to four times as high in the offspring of alcoholics as in appropriate comparison subjects (52, 67, 68). Although the age at first drink is likely to be in the early to mid-teens (similar to that for the general population), major alcohol problems often do not appear until the 20s or 30s for most people with primary alcohol dependence (69). On the other hand, the age at onset for most major anxiety disorders is before age 30 (30). Therefore, if individuals at high risk for alcoholism were likely to develop their alcohol abuse or dependence as a complication of preexisting anxiety disorders or if anxiety and alcohol-related disorders were genetically associated or linked, one would expect that the offspring of alcoholics would have higher

TABLE 4. Studies of Social Phobia Among Alcoholics^a

Study	Number of Alcoholic Subjects	Stage of Alcoholism Treatment	Social Phobia		
			Total Rate (%)	Social Phobia Preceded Alcoholism (%)	Adjusted Rate (%) ^b
Bowen et al. (56)	48	After 5-7 days of abstinence	8	—	2-4
Chambless et al. (57)	75	After detoxification	19	80	15
Mullaney and Trippett (64)	102	After 10 days of abstinence	24	—	6-12
Smail et al. (65)	60	After 2 weeks of abstinence	39	—	10-20
Stravynski et al. (44)	96	After 2 weeks of abstinence	8	70	6
Weiss and Rosenberg (43)	84	After detoxification	2	60	1
Overall	465	—	—	—	9 ^c

^aGeneral population lifetime rates: Kushner et al. (7): 2%; Regier et al. (4): 3%; Kessler et al. (63): 13% overall, 11% for males.

^bPossibly independent of the temporary effects of alcohol.

^cMean value.

TABLE 5. Studies of Generalized Anxiety Disorder Among Alcoholics^a

Study	Number of Alcoholic Subjects	Stage of Alcoholism Treatment	Generalized Anxiety Disorder		
			Total Rate (%)	Generalized Anxiety Disorder Preceded Alcoholism (%)	Adjusted Rate (%) ^b
Bowen et al. (56)	48	After 5-7 days of abstinence	23	—	6-12
Ross et al. (42)	370	—	56	49	27
Weiss and Rosenberg (43)	84	After detoxification	8	60	5
Overall	502	—	—	—	22 ^c

^aGeneral population rates: Kushner et al. (7): 6%; Robins et al. (62): 9%; Kessler et al. (63): 5% overall, 4% for males.

^bPossibly independent of the temporary effects of alcohol.

^cMean value.

than normal rates of anxiety disorders before the onset of alcohol dependence.

There are data indicating that children of alcohol-dependent men and women show high rates of a variety of *symptoms* during childhood (70-73). These data, frequently including children of parents with drug dependence and/or antisocial personality disorder, document high levels of impulsiveness and low self-concept among children of these groups (35, 54, 74-76). Such studies also suggest a higher than normal prevalence of conduct disorder, oppositional disorder, and/or attention deficit disorder in children of alcoholics. However, once the impact of antisocial personality disorder is controlled, this finding regarding attention deficit disorder might no longer hold (77-82).

Despite the findings of a high level of anxiety *symptoms* in some, but not all, studies of children of alcoholics, few prospective studies have demonstrated that these offspring have a higher than expected rate of diagnosable anxiety *disorders*. For example, an evaluation of adolescents from families with alcoholism in multiple generations indicated that the rates of diagnosable anxiety disorders were no higher than those for comparison subjects (35). Similarly, a campus survey of 18-21-year-old sons of alcoholics and comparison subjects demonstrated no difference in risk for any major psychiatric syndromes between groups (83). Also, a recently completed 10-year follow-up of sons of alcoholics and men with negative family histories who were originally evaluated at about age 20 revealed no greater risk for any major anxiety disorder in the individuals at higher risk for the future

development of alcoholism (84). Further, support for the conclusion that a family history of alcoholism does not increase the risk for anxiety disorders comes from an evaluation of young children of alcoholics and comparison subjects at age 3 (85). A study of identical twins of alcoholics revealed that their risk for anxiety symptoms is no higher than normal except in the context of heavy drinking (49). The series of studies of children of alcoholics and comparison subjects from a Danish population, identifying children soon after birth and following them into their 30s, did not indicate a higher than expected risk for anxiety disorders independent of alcoholism in the children of alcoholics, despite their demonstrated higher prevalence of alcohol use disorders at follow-up (86, 87). Although a slightly higher rate of anxiety diagnoses was seen in the children of alcoholics than in the comparison subjects (13% versus 5%) at age 30, such diagnoses were primarily seen among subjects with active alcohol dependence. Of this group, 41% met criteria for antisocial personality disorder and many had abused drugs other than alcohol (86). This same group did *not* have higher rates of anxiety disorders at age 20, raising the possibility that the anxiety symptoms observed a decade later may have resulted from temporary organic anxiety syndromes. Finally, a recent evaluation of psychopathology in 125 children of alcoholics and comparison subjects at age 6 to 18 years failed to reveal high rates of any psychiatric diagnoses except oppositional and conduct disorders in the children of alcoholics (73).

On the other hand, one recent cross-sectional study of adults with "alcoholic parents" showed high lifetime

risks, relative to those for comparison subjects, of generalized anxiety disorder (15% versus 8%), panic disorder (3% versus 1%), simple phobia (15% versus 11%), and agoraphobia (9% versus 5%) but no difference in the rate of social phobia (88). These results are potentially important and need replication with additional, older populations. However, this study, which grew out of the Epidemiological Catchment Area program, suffers from most of the problems we listed earlier in this paper. The impact of comorbid conditions (e.g., substance use disorders) was not controlled; all anxiety syndromes were counted, including those that might be present in the context of substance use; multiple diagnoses were included with no hierarchy, so that the same person was counted for multiple anxiety syndromes, resulting in potentially inflated rates for some disorders; and family history data were not considered.

Thus, while some psychiatric *symptoms* occur at higher than expected rates in children of alcoholics, especially adult children of alcoholics who seek help (74, 89), all but one of the studies cited offer little support for a high risk of major diagnosable anxiety disorders among a more representative cross section of offspring of alcoholic parents. This is true in most cross-sectional and longitudinal studies of children of alcoholics from Scandinavia and the United States and even among children of alcoholics who later developed alcohol dependence themselves. However, four of the seven studies included evaluated people before age 21, and additional work will be needed to follow these groups into middle age before more definite conclusions can be drawn.

Follow-Up of Alcoholics After Abstinence

The rates of anxiety disorders among alcoholics described in the section "Anxiety Disorders Among Alcohol-Dependent Individuals" were difficult to interpret because of the impact of acute and protracted withdrawal syndromes (17, 64). Acute withdrawal symptoms, including heightened feelings of anxiety, panic attacks, and phobic behaviors, are most likely to appear during the first week of abstinence. Symptoms of autonomic overactivity and anxiety as part of a protracted withdrawal syndrome are likely to be most intense over the first few weeks to months, and they then decrease in intensity (17-19). Thus, a more accurate reflection of an association between anxiety disorders and alcoholism might accrue from longer-term prospective evaluations of alcohol-dependent individuals.

Our own group recently completed a 1-year follow-up of 239 men with primary alcohol dependence (12, 16, 90). The 1-year follow-up included structured diagnostic interviews, focusing on diagnosable DSM-III-R psychiatric syndromes since discharge, administered separately to the subject and to a knowledgeable resource person. This study indicated a higher than expected rate of anxiety *symptoms* (not diagnosable disorders) among alcoholics who subsequently returned to heavy drinking, but it did not show a high rate of anxiety *disorders* in subjects who remained abstinent.

Consistent with these findings are the results of several other longitudinal evaluations of alcoholics. Even in the context of high levels of anxiety or affective symptoms soon after the beginning of treatment, these symptoms continued to improve if abstinence was maintained (24-29). However, the paucity of such longitudinal studies mandates that more investigations of this type be carried out before final conclusions are drawn.

Alcoholism Among Subjects With Anxiety Disorders

If anxiety disorders and alcoholism are causally related, there should be a high rate of alcoholism among patients being treated for anxiety disorders. Two older studies (91, 92) of the prevalence of alcoholism in patients being treated for anxiety neurosis were identified. These investigations suggest a lifetime population prevalence of alcohol abuse/dependence of approximately 14%. Even though the studies by Torgersen (91) and by Cloninger et al. (92) used different methods for determining the level of alcohol problems, the rates of alcoholism observed in the anxiety disorder patients were consistent with the population prevalence estimates (2, 7, 62).

Five studies (92-96) examined the frequency of alcoholism in panic disorder patients. Most studies showed a rate of alcoholism similar to that found in the general population, approximately 14%-16%. The exception is the study by Reich and Chaudry (93), who found that 17 (28%) of 61 panic disorder patients in a drug treatment study were retrospectively found to have a lifetime history of alcoholism. These subjects were recruited through newspaper advertisements to participate in a study of the effectiveness of alprazolam for panic symptoms. This apparent excess of alcoholism in panic disorder patients might be accurate for this study group. However, these patients with comorbid disorders might have been attracted to a study that offered relief from their panic symptoms. Often persons with substance use disorders do not come to treatment because of the substance abuse problem alone; they seek relief from its associated temporary features, such as depression or anxiety.

Data on the rate of alcoholism in social phobia patients can be found in two reports (96, 97). Both seem to suggest that alcoholism is highly prevalent among patients with social phobia (i.e., 20%-30%). However, in the Amies et al. study (97) alcoholism was defined as occurring when alcohol was "taken in excess," while in the Thyer et al. study (96) alcoholism was defined as a MAST score higher than 5. As indicated previously, the specificity of the MAST for determining alcohol dependence is low. Thus, the rates of alcoholism in these two studies may have been overestimated.

The prevalence of alcoholism among agoraphobic patients has also been examined. Studies by Amies et al. (97), Marks et al. (98), and Breier et al. (99) showed the rate of alcoholism to be close to population prevalence rates (7%-17%). Of particular note are the studies by Bibb and Chambless (100) and by Thyer et al. (96). In the Bibb and Chambless study 21% of agoraphobic outpatients had "alcoholism" as defined by means of a self-report

using the MAST. The rate of alcoholism fell from 21% to 13% when formal DSM-III criteria were applied. Similarly, the Thyer et al. study also used the MAST to define a case of alcoholism. It should also be noted that in the Amies et al. study anxiety symptoms and the quantity of alcohol used were recorded for subjects but formal criteria were not applied for either the diagnosis of agoraphobia or the definition of alcoholism.

In general, then, most published studies of alcoholism in patients with anxiety disorders do not show a marked excess of alcoholism over population prevalence rates. In the few studies that do, the excess may relate to important subgroups that require further study. However, the use of inappropriate diagnostic criteria for identifying a case or the use of especially high-risk patients might have contributed the few positive results.

Familial Crossover Between Alcoholism and Anxiety Disorders

Is there a family crossover—that is, is there a higher than expected prevalence of alcoholism in the biological relatives of anxiety disorder probands and vice versa? To answer this question, two additional methodological issues must be considered. First, the distinction between family history and family study methods must be recognized. Through the family history method one obtains data about biological relatives only from an informant—usually the proband. This person may not have direct knowledge of the target individual and may rely on hearsay with respect to the information provided. This method frequently has low sensitivity and specificity with respect to many psychiatric disorders that are not typically associated with more extreme forms of behavioral dysfunction. The family study method involves direct interviews of all available biological relatives. Thus, detailed information can be obtained directly from the target individual. The second consideration is that the prevalences observed for different psychiatric disorders must be corrected for the ages of the subjects examined in order to determine the morbid risks. The age at which a person is most likely to become affected (i.e., the age of risk) varies across different psychiatric disorders. Therefore, the proportion of biological relatives who are not at risk, who have entered the risk period, or who have passed through the risk period varies according to the age of the individual family members and according to the particular disorder of interest. A number of age-correction methods are available, e.g., the Stromgren method. Age corrections are often necessary for making accurate comparisons of subject groups from multigeneration families or obtained from different populations.

Several studies (92–96) have examined the families of patients with panic disorder. Only two groups of investigators have reported rates of alcoholism in these biological family members that are higher than population prevalence rates. Crowe et al. (101) found a slightly higher than expected rate of alcoholism (18%), while

Leckman et al. (102) reported a lifetime prevalence of 21% in the family members of probands with major depression and panic disorder. However, the rate of alcoholism dropped to approximately 16% when the families of probands who themselves also had alcoholism were excluded. Further, the rate of alcoholism among the biological relatives of probands with either depression plus generalized anxiety disorder or depression plus agoraphobia was approximately 11% with this exclusion. An additional two studies centering on panic disorder (91, 92) showed rates of alcoholism among both male and female relatives that were similar to or less than the population prevalence of alcoholism. In one of these (91) the family history method (versus direct interview) was used to examine the rates of alcoholism in family members of anxiety disorder patients.

The family members of patients with phobic disorders have also been studied with respect to the lifetime prevalence of alcoholism (103–105). Munjack and Moss (103) reported that 27% of the relatives of agoraphobic probands had a lifetime history of alcoholism, compared to 20% of the relatives of probands with social phobia. It should be noted that in the Munjack and Moss study the interviews with the relatives were conducted over the telephone, and the diagnosis of alcoholism was inferred and presumed on the basis of chronic alcohol problems in a first-degree relative as reported by the index subject. The more methodologically sound study by Noyes et al. showed similar rates of alcohol disorders in relatives of patients with panic disorder (7%) and comparison subjects (4%) but did give a rate of 13% for relatives of agoraphobics (104). Harris et al. (105) reported a prevalence of 30% among the male relatives of 20 agoraphobic probands. The overall morbid risk for alcoholism was found to be 18% among the male relatives of the 20 probands with panic disorder, compared to 10% of the male relatives of comparison subjects. It should also be noted that 35% of the probands also had diagnoses of substance use disorders. A recent direct interview family study of social phobia by Fyer et al. (106) failed to indicate any difference in the prevalence of alcohol abuse in the biological family members of the probands and in relatives of never-ill comparison subjects (5% versus 4%).

Of course, there are additional data of interest. One investigation evaluated the rate of “alcohol disorders” among relatives of individuals with generalized anxiety disorder, finding a morbid risk of 6% in the family members of the anxiety disorder patients and a morbid risk (age corrected) of 4% in the families of surgical comparison patients (107). Unfortunately, few studies have adequately investigated the rate of alcohol use disorders in relatives of individuals with other major anxiety syndromes.

Only a limited number of investigations have evaluated the risk of lifelong major anxiety disorders in the relatives of alcohol-dependent men and women. Merikangas et al. (108), in a study evaluating the crossover between *depression* and anxiety disorders, also evaluated the familial rate of alcohol use disorders. The

authors reported that 5% of the relatives of a comparison group had one of the anxiety disorders, while the same was true for 20% of the relatives of a small subgroup of study subjects who themselves had both alcoholism and depression. The study methods were thorough, and the results are worthy of further evaluation. However, a substantial proportion of the relatives had antisocial personality disorder, which is associated with a chaotic lifestyle and high risk for drug dependence; the anxiety disorders reported included simple phobia, a common condition that is not thought to be a severe psychiatric disorder; and the co-occurrence of depression makes it difficult to establish the rates of alcoholism in the relatives of subjects who demonstrated only anxiety disorders. Even with these considerations, however, the study raises the question of some level of familial crossover for anxiety and alcohol use disorders in those complex patients.

In a recent study structured personal interviews were used to evaluate the rate of major psychiatric disorders in 605 interviewed first-degree relatives of alcohol-dependent men and women (40). After the potential impact of temporary anxiety syndromes in the context of their own alcohol or other drug use disorders was controlled for and after the data were analyzed separately following consideration of assortative mating, the rates of disorders among these interviewed relatives included 3% for panic disorder, 1% for agoraphobia, 2% for social phobia, and 1% for obsessive-compulsive disorder, yielding an overall rate of any major anxiety disorder in first-degree relatives of 7%. These results are not exceptionally higher than those expected in the general population.

In general, then, a review of the literature does not indicate a consistent family crossover between alcoholism and anxiety disorders once morbidity in the proband is controlled for and appropriate assessment methods and criteria are used. However, several of the investigators suggested that a modest level of crossover might be seen in some pedigrees. These results deserve further study.

Longitudinal Studies

Longitudinal prospective studies provide the best opportunity to follow the relationship between alcoholism and anxiety disorders over time and to document which disorder occurs first. With this approach, subjects are directly assessed before the onset of any disorder and are followed prospectively through the period of risk. Two published studies have directly examined the relationship of alcoholism to anxiety disorders in general population samples. The study by Hagnell and Tunvia (109) is a continuation of Essen-Moller's study of the Lundby, Sweden, population. Personal interviews were conducted with 99% of the 950 men aged 20 years of age or older. No differences were found between men with alcoholism and those without alcoholism in terms of the population prevalence of anxiety disorders. This relationship held regardless of the severity (abuse, ad-

diction, chronic) of the alcoholism studied. Ensminger et al. (110) reported data from the Woodlawn study on the relationship between levels of anxiety symptoms and the frequency of beer, liquor, marijuana, and cigarette use. However, the emphasis on symptoms rather than diagnoses makes the impact of this study only marginal. The sample of 16-17-year-old boys and girls participated in this prospective study for more than 10 years. The correlation between anxiety symptoms and substance use for both boys and girls was almost negligible (range, $r=0.10$ to $r=-0.10$). Similar findings have been reported by Kammeier et al. (111). Vaillant (47) has followed two groups of young men from adolescence into late adult life. He reported, "Prospective data from both the Core City and the College samples suggest that premorbidly anxious individuals were not at increased risk for alcoholism" (p. 77). He added, "In dismissing . . . depression and anxiety from major etiological consideration, [this is not to say they are of no importance in alcoholism]. These factors will make any chronic condition worse" (p. 311). He did not present the data supporting these statements. In summary, while the majority of the studies in this category do not suggest a close tie between lifelong anxiety disorders and alcoholism, there have been too few investigations to indicate any final conclusions.

DISCUSSION

There is little controversy regarding the conclusion that alcoholic men and women are more likely to demonstrate clinically relevant anxiety symptoms than are members of the general population. These symptoms include phobic behaviors, conditions that resemble generalized anxiety disorder, and repetitive panic attacks. Most clinicians would agree that when such symptoms are seen, it is important to take a number of common-sense clinical steps. Patients should be carefully evaluated for possible medical problems and psychiatric disorders that might have contributed to the anxiety symptoms, they should be reassured regarding the ability of the clinician to help them deal with these symptoms, and education and behavioral approaches aimed specifically at diminishing the symptoms should be offered (8).

However, the high prevalence of these anxiety symptoms does not necessarily mean that these alcoholic individuals will demonstrate the long-term course or require the long-term treatments associated with DSM-III-R major anxiety disorders. When one turns to six types of studies in the literature, there are contradictory conclusions. However, no one type of study alone is methodologically rigorous enough to yield definitive answers.

Tables 1 through 5 do not support the conclusion that the majority, or even a large minority, of alcoholics have lifelong major anxiety disorders. In this critical review of the literature, the evidence in these tables that might suggest a relationship relates to panic disorder; perhaps 6% to 7% of alcohol-dependent individuals

might demonstrate an independent DSM-III-R panic syndrome. These figures are at least twice as high as those reported for the general population, although it is possible that the diagnosis among some alcoholics might represent continued alcohol-induced anxiety symptoms that did not predate the alcohol use disorder. Less impressive evidence is offered regarding a possible relationship between alcoholism and social phobia or generalized anxiety disorder. While the rate of anxiety disorders among alcoholics is a good deal lower than estimates given in some of the individual studies often cited in the literature, the possibility that an important minority of alcohol-dependent men and women might have independent lifelong major anxiety disorders, especially panic disorder, must be carefully entertained in future investigations. Yet the data do not justify a conclusion by clinicians that a large proportion of alcoholics really have lifelong panic disorder syndromes that must be treated.

Less impressive support for a relationship between anxiety and alcohol use disorders comes from an evaluation of the rate of alcoholism among patients with major anxiety syndromes. In contrast to the first type of investigation, most of the studies do not convincingly demonstrate higher rates of alcoholism (defined differently in different studies) among patients with anxiety disorders, even among those with panic disorder. While the few studies that have addressed the rate of alcoholism among individuals with social phobia deserve further consideration, none of the other major anxiety disorders appears to be common enough to support an overall close relationship between anxiety disorders and alcohol use disorders.

The potential relationships demonstrated from the first two types of studies must not be ignored, but neither prospective investigations of alcoholics or general population groups over time nor careful studies of children of alcohol-dependent individuals support an overall close tie between alcoholism and DSM-III-R major anxiety diagnoses. At the same time, despite the overall methodological rigor of these types of investigations, they do suffer from inconsistencies in the definitions of syndromes across studies. Additional difficulties here include the relative youth of many of the individuals incorporated in studies of children of alcoholics, as well as the small number of investigations of alcoholics over time. Finally, the last type of study reviewed, an evaluation of the familial crossover between alcohol use disorders and major anxiety disorders, offers no clearer conclusions. Most of these investigations were relatively negative or equivocal regarding a relationship. However, two of five investigations examining panic disorder indicated a slight, but possibly significant, familial crossover between the two types of syndromes.

When faced with inconclusive data, we can draw only limited conclusions. It is our belief that the high rates of panic disorder, social phobia, and generalized anxiety disorder among alcoholics (tables 1, 4, and 5) are likely to apply to only a relatively small group of alcohol-dependent men and women. Our own interpretation of

this literature review suggests that even the adjusted figures in the tables might be exaggerated by problems in retrospective reporting of data and by the presence of symptoms of both acute and protracted withdrawal syndromes. We believe that if an excessively close relationship between anxiety disorders and a future risk for alcohol dependence existed, evaluations of children of alcoholics and longitudinal studies of individuals would have revealed more impressive results.

In considering these data, it is important to recognize that our own critical review of the literature suffered from several problems that could not be appropriately controlled. It is hoped that in future work in the six arenas we have outlined, closer attention will be paid to potential differences in anxiety and substance use disorders between men and women. In addition, optimal interpretation of data from any of these studies will require intensive efforts to establish an appropriate group of comparison subjects. Third, the most convincing data will require age corrections for the reported rates of both anxiety and alcohol use disorders. We also believe that in the future, emphasis must be placed on prospective evaluations of individuals with either of the two types of disorders under consideration and on longitudinal studies of their offspring. Finally, appropriate methods should be used to evaluate separately data regarding probands who did and did not complete treatment programs, as this factor could be related to personal and familial rates of comorbidity.

In conclusion, the relationship between symptoms of anxiety and alcohol use disorders is complex. Investigators must consider several important factors in interpreting these earlier studies. Similarly, just as clinicians recognize the need to carefully consider various potential organic etiologies for clinical patients that might imply different prognoses and unique treatment needs, it is important to carefully consider the implications of anxiety symptoms among alcoholics. Even syndromes that impair functioning and appear to fulfill diagnostic criteria for anxiety disorders do not necessarily indicate a lifelong anxiety syndrome; they are often temporary substance-induced anxiety symptoms likely to benefit from more short-term interventions.

REFERENCES

1. Hesselbrock MN, Meyer R, Keener JJ: Psychopathology in hospitalized alcoholics. *Arch Gen Psychiatry* 1985; 42:1050-1055
2. Helzer JE, Pryzbeck TR: The co-occurrence of alcoholism with other psychiatric disorders in the general population and its impact on treatment. *J Stud Alcohol* 1988; 49:219-224
3. Weissman MM, Myers JK, Harding PS: Prevalence and psychiatric heterogeneity of alcoholism in a United States urban community. *J Stud Alcohol* 1980; 41:672-681
4. Regier DA, Farmer ME, Rae DS, Locke BZ, Keith SJ, Judd LL, Goodwin FK: Comorbidity of mental disorders with alcohol and other drug abuse. *JAMA* 1990; 264:2511-2518
5. Schuckit MA: Genetic and clinical implications of alcoholism and affective disorder. *Am J Psychiatry* 1986; 143:140-147
6. Schuckit MA: Anxiety disorders and substance abuse, in *American Psychiatric Press Review of Psychiatry*, vol 11. Edited by Tasman A, Riba M. Washington, DC, American Psychiatric Press, 1992

7. Kushner MG, Sher KJ, Beitman BD: The relation between alcohol problems and the anxiety disorders. *Am J Psychiatry* 1990; 147:685-695
8. Schuckit MA: Treatment of anxiety in patients who abuse alcohol and drugs, in *Handbook of Anxiety*, vol 4: The Treatment of Anxiety. Edited by Noyes R, Roth M, Burros GD. Amsterdam, Elsevier, 1990
9. Goodwin DW, Guze SB: *Psychiatric Diagnosis*, 5th ed. New York, Oxford University Press, 1994
10. Schuckit MA: *Drug and Alcohol Abuse: A Clinical Guide to Diagnosis and Treatment*, 3rd ed. New York, Plenum, 1989
11. Brown SA, Schuckit MA: Changes in depression among abstinent alcoholics. *J Stud Alcohol* 1988; 49:412-417
12. Schuckit MA, Irwin M, Brown SA: The history of anxiety symptoms among 171 primary alcoholics. *J Stud Alcohol* 1990; 51:34-41
13. Clark DB, Sayette MA: Anxiety and the development of alcoholism. *Am J Addict* 1993; 2:59-76
14. Selzer M: The Michigan Alcoholism Screening Test: the quest for a new diagnostic instrument. *Am J Psychiatry* 1971; 127:1653-1658
15. Schuckit MA, Irwin M: Diagnosis of alcoholism. *Med Clin North Am* 1988; 72:1133-1153
16. Brown SA, Irwin M, Schuckit MA: Changes in anxiety among abstinent male alcoholics. *J Stud Alcohol* 1991; 52:55-61
17. Satel SL, Kosten TR, Schuckit MA, Fischman MW: Should protracted withdrawal from drugs be included in DSM-IV? *Am J Psychiatry* 1993; 150:695-704
18. De Soto CB, O'Donnell WE, Allred LJ, Lopes CE: Symptomatology in alcoholics at various stages of abstinence. *Alcohol Clin Exp Res* 1985; 9:505-512
19. Roelofs SM, Dikkenberg GM: Hyperventilation and anxiety: alcohol withdrawal symptoms decreasing with prolonged abstinence. *Alcohol* 1987; 4:215-220
20. Stockwell T, Bolderston H: Alcohol and phobias. *Br J Addict* 1987; 82:971-979
21. Aneshensel CS, Huba GJ: Depression, alcohol use, and smoking over one year: a four-wave longitudinal causal model. *J Abnorm Psychol* 1983; 92:134-150
22. Gibson S, Becker J: Changes in alcoholics' self-reported depression. *Q J Stud Alcohol* 1973; 34:829-836
23. Tamerin JS, Weiner S, Mendelson JH: Alcoholics' expectancies and recall of experiences during intoxication. *Am J Psychiatry* 1970; 126:1697-1704
24. Liskow B, Mayfield D, Thiele J: Alcohol and affective disorder: assessment and treatment. *J Clin Psychiatry* 1982; 43:144-147
25. Pettinati HM, Sugerman A, Maurer HS: Four year MMPI changes in abstinent and drinking alcoholics. *Alcohol Clin Exp Res* 1982; 6:487-494
26. Keeler MH, Taylor CI, Miller WC: Are all recently detoxified alcoholics depressed? *Am J Psychiatry* 1979; 136:586-588
27. Goldman DS, Bander KW: Six-month course of depression in female alcoholics. *J Subst Abuse* 1990; 2:375-380
28. Mossberg D, Liljeberg P, Borg S: Clinical conditions in alcoholics during long-term abstinence: a descriptive, longitudinal treatment study. *Alcohol* 1985; 2:551-553
29. Hatsukami D, Pickens RW: Posttreatment depression in an alcohol and drug abuse population. *Am J Psychiatry* 1982; 139:1563-1566
30. Angst J, Vollrath M: The natural history of anxiety disorders. *Acta Psychiatr Scand* 1991; 84:446-452
31. Schuckit MA, Tipp JE, Kelner E: Are daughters of alcoholics more likely to marry alcoholics? *Am J Drug Alcohol Abuse* 1994; 20:237-245
32. Vanderberg SG: Assortative mating or who marries whom? *Behav Genet* 1972; 2:127-157
33. Merikangas KR, Prusoff BA, Weissman MM: Parental concordance for affect disorders: psychopathology in offspring. *J Affect Disord* 1988; 15:279-290
34. Merikangas KR: The genetic epidemiology of alcoholism. *Psychol Med* 1990; 20:11-22
35. Hill SY: Personality characteristics of sisters and spouses of male alcoholics. *Alcohol Clin Exp Res* 1993; 17:733-739
36. Hall RL, Hesselbrock VM, Stabenau JR: Familial distribution of alcohol use, 1: assortative mating in the parents of alcoholics. *Behav Genet* 1983; 13:361-372
37. Stabenau J, Hesselbrock V: Assortative mating, family pedigree and alcoholism. *Substance and Alcohol Misuse/Abuse* 1980; 1:375-382
38. Weissman MM, Myers JK: Clinical depression in alcoholism. *Am J Psychiatry* 1980; 137:372-373
39. Zisook S, Schuckit MA: Male primary alcoholics with and without family histories of affective disorder. *J Stud Alcohol* 1987; 48:337-344
40. Schuckit MA, Hesselbrock VM, Tipp J, Nurnberger JI, Anthenelli RM, Crowe RR: The prevalence of major anxiety disorders in relatives of alcohol dependent men and women. *J Stud Alcohol* (in press)
41. Norton CR, Malan J, Cairns SL, Wozney KA: Factors influencing drinking behavior in alcohol panickers and non-panickers. *Behav Res Ther* 1989; 27:167-171
42. Ross HE, Glaser FB, Germanson T: The prevalence of psychiatric disorders in patients with alcohol and other drug problems. *Arch Gen Psychiatry* 1988; 45:1023-1031
43. Weiss KJ, Rosenberg DJ: Prevalence of anxiety disorder among alcoholics. *J Clin Psychiatry* 1985; 46:3-5
44. Stravynski A, Lamontagne Y, Lavallee YJ: Clinical phobias and avoidant personality disorder among alcoholics admitted to an alcoholism rehabilitation setting. *Can J Psychiatry* 1986; 31:714-719
45. Atkinson JH, Slater MA, Patterson TL, Grant I, Garfin SR: Prevalence, onset, and risk of psychiatric disorders in men with chronic low back pain: a controlled study. *Pain* 1991; 45:111-121
46. Morrissey ER, Schuckit MA: Stressful life events and alcoholism among women seen at a detoxification center. *J Stud Alcohol* 1978; 39:1559-1576
47. Vaillant G: *The Natural History of Alcoholism*. Cambridge, Mass, Harvard University Press, 1983
48. Vaillant G: Some differential effects of genes and environment of alcoholism, in *Alcoholism: Origins and Outcome*. Edited by Rose RM, Barrett J. New York, Raven Press, 1988
49. Mullan MJ, Gurling HMD, Oppenheim BE, Murray RM: The relationship between alcoholism and neurosis: evidence from a twin study. *Br J Psychiatry* 1988; 148:435-441
50. Anthenelli RM, Smith TL, Irwin MR, Schuckit MA: A comparative study of criteria for subgrouping alcoholics: the primary/secondary diagnostic scheme versus variations of the type 1/type 2 criteria. *Am J Psychiatry* 1994; 151:1468-1474
51. Hesselbrock VM, Hesselbrock MN, Workman-Daniels KL: Effect of major depression and antisocial personality on alcoholism: course and motivational patterns. *J Stud Alcohol* 1986; 47:207-212
52. Schuckit MA: A clinical model of genetic influences in alcohol dependence. *J Stud Alcohol* 1994; 55:5-17
53. Reich W, Earls F, Powell J: A comparison of the home and social environments of children of alcoholic and non-alcoholic parents. *Br J Addict* 1988; 83:831-839
54. Velleman R, Orford J: The importance of family discord in explaining childhood problems in the children of problem drinkers. *Addiction Res* 1993; 1:39-57
55. Russell M, Czarnecki DM, Cowan R, McPherson E, Mudar PJ: Measures of maternal alcohol use as predictors of development in early childhood. *Alcohol Clin Exp Res* 1991; 15:991-1000
56. Bowen RC, Cipywnyk D, D'Arcy C, Keegan D: Alcoholism, anxiety disorders, and agoraphobia. *Alcohol Clin Exp Res* 1984; 8:48-50
57. Chambless DL, Cherney J, Caputo GC, Rheinstein BJG: Anxiety disorder and alcoholism: a study with inpatient alcoholics. *J Anxiety Disorder* 1987; 1:29-40
58. Cox BJ, Norton CR, Dorward J, Fergusson PA: The relationship between panic attacks and chemical dependencies. *Addict Behav* 1989; 14:53-60
59. Nunes E, Quitkin F, Berman C: Panic disorder and depression in female alcoholics. *J Clin Psychiatry* 1988; 49:441-443
60. Powell BJ, Penick EC, Othmer E, Bingham SF, Rice AS: Preva-

- lence of additional psychiatric syndromes among male alcoholics. *J Clin Psychiatry* 1982; 43:404-407
61. Robins LN, Helzer JE, Weissman MM, Orvaschel H, Gruenberg E, Burke JD, Regier DA: Lifetime prevalence of specific psychiatric disorders in three sites. *Arch Gen Psychiatry* 1984; 41:949-958
 62. Robins LN, Locke BZ, Regier DA: An overview of psychiatric disorders in America, in *Psychiatric Disorders in America*. Edited by Robins LN, Regier DA. New York, Free Press, 1991
 63. Kessler RC, McGonagle KA, Zhao S, Nelson CB, Hughes M, Eshleman S, Wittchen H, Kendler KS: Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. *Arch Gen Psychiatry* 1994; 51:8-19
 64. Mullaney JA, Trippett CJ: Alcohol dependence and phobias: clinical description and relevance. *Br J Psychiatry* 1979; 135: 565-573
 65. Smail P, Stockwell T, Canter S, Hodgson R: Alcohol dependence and phobic anxiety states, I: a prevalence study. *Br J Psychiatry* 1984; 144:53-57
 66. Sellers EM, Kalant H: Alcohol intoxication and withdrawal. *N Engl J Med* 1976; 24:757-762
 67. Devor E, Cloninger CR: Genetics of alcoholism. *Annu Rev Genet* 1989; 23:19-36
 68. Begleiter H, Porjesz B: Potential biological markers in individuals at high risk for developing alcoholism. *Alcohol Clin Exp Res* 1988; 12:488-493
 69. Schuckit MA, Smith TL, Anthenelli R, Irwin M: The clinical course of alcoholism in 636 male inpatients. *Am J Psychiatry* 1993; 150:786-792
 70. El-Guebaly N, Offord DR: The offspring of alcoholics: a critical review. *Am J Psychiatry* 1977; 134:357-365
 71. Jacob T, Favorini A, Meisel SS, Anderson CM: The alcoholic's spouse, children and family interactions. *J Stud Alcohol* 1978; 39:1231-1251
 72. Moos R, Billings AG: Children of alcoholics during the recovery process: alcoholic and matched control families. *Addict Behav* 1982; 7:155-163
 73. Reich W, Earls F, Frankel O, Shayka JJ: Psychopathology in children of alcoholics. *J Am Acad Child Adolesc Psychiatry* 1993; 32:995-1002
 74. Tweed SH, Ryff CD: Adult children of alcoholics: profiles of wellness amidst distress. *J Stud Alcohol* 1991; 52:133-141
 75. Jacob T, Leonard K: Psychosocial functioning in children of alcoholic fathers, depressed fathers and control fathers. *J Stud Alcohol* 1986; 47:373-380
 76. Beardslee WR, Son L, Vaillant GE: Exposure to parental alcoholism during childhood and outcome in adulthood: a prospective longitudinal study. *Br J Psychiatry* 1986; 149:584-591
 77. Schuckit MA, Sweeney S, Huey L: Hyperactivity and the risk for alcoholism. *J Clin Psychiatry* 1987; 48:275-277
 78. Mannuzza S, Klein RG, Konig PH, Giampino TL: Hyperactive boys almost grown up, IV: criminality and its relationship to psychiatric status. *Arch Gen Psychiatry* 1989; 46:1073-1079
 79. Mannuzza S, Klein RG, Bonagura N, Malloy P, Giampino TL, Addali KA: Hyperactive boys almost grown up, V: replication of psychiatric status. *Arch Gen Psychiatry* 1991; 48:77-83
 80. Earls F, Reich W, Jung KG, Cloninger CR: Psychopathology in children of alcoholic and antisocial parents. *Alcohol Clin Exp Res* 1988; 12:481-487
 81. Hechtman I, Weiss G, Perlman MS: Hyperactive as young adults: past and current substance abuse and antisocial behavior. *Am J Orthopsychiatry* 1984; 54:415-425
 82. Gittelman R, Mannuzza S, Shenker R, Bonagura N: Hyperactive boys almost grown up, I: psychiatric status. *Arch Gen Psychiatry* 1985; 42:937-947
 83. Schuckit MA: A study of young men with alcoholic close relatives. *Am J Psychiatry* 1982; 139:791-794
 84. Schuckit MA: Low level of response to alcohol as a predictor of future alcoholism. *Am J Psychiatry* 1994; 151:184-189
 85. Fitzgerald HE, Sullivan LA, Ham HP, Zucker RA, Brucker S, Noll RB: Predictors of behavior problems in three-year-old sons of alcoholics: early evidence for the onset of risk. *Child Dev* 1993; 64:110-123
 86. Knop J, Goodwin DW, Jensen P, Penick E, Pollock V, Gabrielli W, Teasdale TW, Mednick SA: A 30-year follow-up study of the sons of alcoholic men. *Acta Psychiatr Scand Suppl* 1993; 370:48-53
 87. Goodwin DW, Schulsinger F, Hermansen L, Guze SB, Winokur G: Alcohol problems in adoptees raised apart from alcoholic biological parents. *Arch Gen Psychiatry* 1973; 28:238-243
 88. Mathew RJ, Wilson WH, Blazer DG, George LK: Psychiatric disorders in adult children of alcoholics: data from the Epidemiologic Catchment Area project. *Am J Psychiatry* 1993; 150: 793-800
 89. Finn PR, Kleinman I, Pihl RO: The lifetime prevalence of psychopathology in men with multigenerational family histories of alcoholism. *J Nerv Ment Dis* 1990; 178:500-504
 90. Schuckit MA, Irwin M, Smith TL: One-year incidence rate of major depression and other psychiatric disorders in 239 alcoholic men. *Addiction* 1994; 87:441-445
 91. Torgersen S: Childhood and family characteristics in panic and generalized anxiety disorders. *Am J Psychiatry* 1986; 143:630-632
 92. Cloninger CR, Martin RL, Clayton P, Guze SB: A blind follow-up and family study of anxiety neurosis: preliminary analysis of the St Louis 500, in *Anxiety: New Research and Changing Concepts*. Edited by Klein DF, Rabkin J. New York, Raven Press, 1981
 93. Reich J, Chaudry D: Personality of panic disorder alcohol abusers. *J Nerv Ment Dis* 1987; 175:224-228
 94. Winokur G, Holeman E: Chronic anxiety neurosis: clinical and sexual aspects. *Acta Psychiatr Scand* 1963; 39:384-412
 95. Woodruff RA, Guze SB, Clayton PJ: Anxiety neurosis among psychiatric outpatients. *Compr Psychiatry* 1972; 13:165-170
 96. Thyer BA, McNece CA, Miller MA: Alcohol abuse among agoraphobics. *Alcoholism Treatment Quarterly* 1987; 4:61-67
 97. Amies PL, Gelder MG, Shaw PM: Social phobia: a comparative clinical study. *Br J Psychiatry* 1983; 142:174-179
 98. Marks IM, Bibley TL, Gelder MG: Modified leucotomy in severe agoraphobia: a controlled social inquiry. *Br J Psychiatry* 1966; 112:757-769
 99. Breier A, Charney DS, Heninger GR: Agoraphobia with panic attacks: development, diagnostic stability, and course of illness. *Arch Gen Psychiatry* 1986; 43:1029-1036
 100. Bibb JL, Chambless DL: Alcohol use and abuse among diagnosed agoraphobics. *Behav Res Ther* 1986; 24:49-58
 101. Crowe RR, Noyes MD, Pauls D, Slymen D: A family study of panic disorder. *Arch Gen Psychiatry* 1983; 40:1065-1069
 102. Leckman JF, Weissman MW, Merikangas KR, Pauls DL, Prusoff BA: Panic disorder and major depression. *Arch Gen Psychiatry* 1983; 40:1055-1060
 103. Munjack DJ, Moss HB: Affective disorder and alcoholism in families of agoraphobics. *Arch Gen Psychiatry* 1981; 38:869-871
 104. Noyes R, Crowe RR, Harris EL, Hamra BJ, McChesney CM, Chaudhry DR: Relationship between panic disorder and agoraphobia. *Arch Gen Psychiatry* 1986; 43:227-232
 105. Harris EL, Noyes R, Crowe R, Chaudhry DR: Family study of agoraphobia. *Arch Gen Psychiatry* 1983; 40:1061-1064
 106. Fyer AJ, Mannuzza S, Chapman TF, Liebowitz MR, Klein DF: A direct interview family study of social phobia. *Arch Gen Psychiatry* 1993; 50:286-293
 107. Noyes R Jr, Clarkson C, Crowe RR, Yates WR, McChesney CM: A family study of generalized anxiety disorder. *Am J Psychiatry* 1987; 144:1019-1024
 108. Merikangas KR, Leckman JF, Prusoff BA, Pauls DL, Weissman MM: Familial transmission of depression and alcoholism. *Arch Gen Psychiatry* 1985; 42:367-372
 109. Hagnell O, Tunvia K: Prevalence and nature of alcoholism in a total population. *Social Psychiatry* 1972; 7:190-201
 110. Ensminger ME, Brown CH, Kellam SG: Social control as an explanation of sex differences in substance use among adolescents, in *Problems of Drug Dependence: NIDA Research Monograph 49*. Edited by Harris L. Washington, DC, National Institute on Drug Abuse, 1983
 111. Kammeier M, Hoffman H, Lopez R: Personality characteristics of alcoholics as college freshmen and at the time of treatment. *Q J Stud Alcohol* 1973; 34:390-399