Follow-up Study of Anxiety Disorder and Alcohol Dependence in Comorbid Alcoholism Treatment Patients

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Background:
Anxiety disorders are present in a high percentage of alcoholism treatment patients. We tested the prediction that having a comorbid anxiety disorder increases the prospective risk for relapse to drinking after alcoholism treatment. We also explored the prospective associations of specific anxiety syndromes (and depression) with drinking and anxiety outcomes.

Methods:
We assessed the diagnostic status and daily drinking patterns of 82 individuals approximately one week after they entered alcoholism treatment (baseline) and again approximately 120 days later (follow-up) (n/1100553).

Results:
Consistent with study predictions, those with a baseline anxiety disorder (approximately 55%) were significantly more likely than others to meet various definitions of drinking relapse over the course of the follow-up. Regression models showed that baseline social phobia was the single best predictor of a return to any drinking after treatment, whereas panic disorder was the single best predictor of a relapse to alcohol dependence after treatment. Having multiple anxiety disorders (versus any specific anxiety disorder) at the baseline was the strongest predictor of having at least one active (“persistent”) anxiety disorder at the follow-up. Cross-sectional analysis at the follow-up showed that anxiety disorder persisted in the absence of a relapse to alcohol dependence far more often than relapse to alcohol dependence occurred in the absence of a persistent anxiety disorder.

Conclusions:
Screening for comorbid anxiety disorder in alcoholism treatment patients is warranted and, where found, should be considered a marker of high relapse risk relative to that of noncomorbid patients. The capacity of specific anxiety treatment to mitigate relapse risk among comorbid patients remains an open question.

Key Words:
Comorbidity, Anxiety Disorder, Alcohol Disorder, Alcoholism, Relapse.

INTRODUCTION

Data from dozens of clinic-based and community-based studies confirm that anxiety disorders and alcohol dependence co-occur at a rate that far exceeds chance (“comorbidity”) (Kushner et al., 2000a; Kushner et al., 1990). The sheer magnitude of comorbidity (e.g., more than 90% of panic disorder and drug dependence cases are comorbid with at least one other lifetime Axis I mental disorder) (Kessler, 1997) raises profound taxonomic issues and complicates greatly the challenge faced by psychopathologists (Brown and Barlow, 1992). Providing an early—and still one of the best—clinical treatise on the concept of comorbidity, Feinstein (1970) argued that a disorder’s course, treatment response, and treatment indications-contraindications could all, in principle, be affected significantly by the presence of a comorbid disorder.

The literature pertaining to the clinical significance of comorbid anxiety disorder in individuals undergoing treatment for alcoholism is sparse, and what literature does exist appears to be contradictory in some respects. On the one hand, there is substantial documentation of decrements in anxiety and depressive symptom levels in the weeks after acute detoxification from alcohol (Brown et al., 1991; Denney and Baugh, 1992; Mossberg et al., 1985). On the other hand, relapse to drinking in the months after treatment tends to be associated with stressful experiences (Brown et al., 1995) and exacerbations of depressed mood and anxiety symptoms (Driessen et al.; 2001; LaBounty et al., 1992; Mossberg et al., 1985; Tomasson and Vaglum, 1996). For example, Tomasson and Vaglum (1998) reported that agoraphobia/panic disorder increased the odds by nearly six-fold of being readmitted after alcohol detoxification among...
individuals with less than two prior admissions. (Polysubstance use was more related to readmission among those with more than three prior admissions.) Similarly, Driessen et al. (2001) found that alcoholism treatment patients with a comorbid anxiety or depressive disorder, as compared with their noncomorbid counterparts, had a significantly greater rate of relapse to drinking within six months of treatment.

A related issue that has also yet to be adequately studied relates to the distinction between independent and dependent anxiety disorders among alcoholics. A common view has been that an onset occurring before that of an alcohol disorder marks a comorbid anxiety disorder that is “independent” of alcohol use and in need of specific treatment, whereas an onset occurring after that of an alcohol disorder marks a comorbid anxiety disorder that is “dependent” on alcohol use and not in need of specific treatment (i.e., beyond abstinence from drinking) (e.g., Allan, 1995). This view has led some to conclude that neither a majority nor even a substantial minority of comorbid alcoholism treatment patients have an independent anxiety disorder requiring specific treatment (e.g., Schuckit and Hesselbrock, 1994). However, Grant et al. (2004) noted that DSM-IV has provided a less restrictive diagnostic algorithm that uses order-of-onset as only one indicator of whether an anxiety syndrome is dependent or independent from a co-occurring alcohol disorder. Operationalizing these DSM-IV criteria in a large epidemiologic survey, Grant et al. (2004) concluded that the vast majority of the anxiety disorders found in the general US population and in alcoholism treatment settings are independent of substance abuse.

Although theirs was a retrospective survey, Grant et al. (2004) recommended prospective designs as providing an ideal vehicle for documenting sequencing of comorbid disorder onset. Kushner et al. (2000a) made a similar point in suggesting that prospectively observing the longitudinal course of comorbid cases after alcoholism detoxification and treatment potentially offers a direct test of whether an anxiety syndrome is or is not dependent on alcohol intoxication and withdrawal; for example, by determining whether the anxiety disorder persists in the absence of ongoing alcohol intoxication and (acute) withdrawal.

In the present study, we sought to address several important questions stemming from the literature just reviewed. The first and central question we addressed is whether having an anxiety disorder when entering an alcoholism treatment program has implications for the likelihood that the treatment will be successful. The primary prediction tested is that having an anxiety disorder at baseline (i.e., beginning of alcoholism treatment) will mark a significantly elevated prospective risk for relapse to drinking by the time of a four-month follow-up assessment. This prediction stems from the empirical findings reviewed above and aligns with the idea that anxiety serves as a drinking cue made potent by past alcohol-induced tension reduction (i.e., negative reinforcement) (e.g., Kushner et al., 2000a; Thomas et al., 2003). A secondary set of questions explored is the extent to which anxiety disorders identified at the baseline persist through to the follow-up. Both the primary and secondary questions are tested with all anxiety disorders collapsed into a single category (to provide maximum statistical power) and also separated into specific anxiety syndromes.

METHODS AND MEASURES

Participants

We recruited participants from the adult (i.e., 18 years and older) acute substance abuse treatment program (i.e., residential treatment lasting approximately 21 consecutive days) at Fairview-University Medical Center in Minneapolis, Minnesota. To be included, patients were required to have a current diagnosis of alcohol dependence according to DSM-IV criteria, based on the Structured Clinical Interview for DSM-IV (First et al., 1989). We also restricted entry into the study to those for whom alcohol was the primary substance of abuse and who reported having regularly consumed alcohol in at least two of the four months before admission. Individuals were excluded if they had a psychotic disorder or a manic episode within the four months preceding the assessment. After a complete description of the study was given to the subjects, written informed consent was obtained.

Recruitment proceeded over a one-year period, during which 1138 patients were admitted to the substance abuse treatment program. Pre-screening resulted in 434 individuals who were qualified for the next stage of screening and indicated an interest in hearing more about the study. Note that the main reasons individuals did not proceed past the initial screening included, in descending order of their frequency: 1) failure to return the screen (“passive refusal”), 2) expressed disinterest in participating (“active refusal”), 3) enrollment in the “nonacute” CT treatment program (evening therapy several days/week) versus the “acute” program (residential full-day treatment), and 4) enrollment in treatment exclusively or primarily for drug versus alcohol disorder. Due to staffing limitations (e.g., breaks over school holidays and limited capacity), we were only able to invite 277 (64%) of these individuals for a final screening assessment. Of those invited for a final screening assessment, 115 attended and 82 were enrolled, including 29 females and 53 males who ranged in age from 18 to 71 years (M = 39.5 years, SD = 10.5 years). From this group, 53 completed the four-month follow-up assessment (35% attrition).

Structured Clinical Interview for DSM-IV

The Structured Clinical Interview for DSM-IV (SCID-IV I/P, Version 2.0) (First et al., 1989) is a semistructured diagnostic interview that determines the presence of specific psychiatric diagnoses during prespecified time frames according to DSM-IV criteria. Trained interviewers ask a series of questions that allow specific diagnostic criteria to be judged as present or absent. Diagnostic decision rules are built into the interview. The SCID was used to document the presence or absence over the last four months at baseline and last month at follow-up of the following anxiety disorders: panic disorder (with or without agoraphobia), agoraphobia without panic attacks, social phobia, obsessive-compulsive disorder (OCD), post-traumatic stress disorder (PTSD), and generalized anxiety disorder. Other psychiatric disorders assessed include major depression and alcohol dependence. Note that the SCID has been shown to have acceptable to good psychometric properties (e.g., Kranzler et al., 1995; Zanarini and Frankenburg, 2001).

SCID: Dating the Order of Comorbid Disorder Onset

We dated the onset of anxiety and alcohol disorders identified during the SCID interview by using the standard SCID questions designed to
elicit this information. If a patient meets diagnostic criteria for panic disorder, for example, the interviewer is then prompted to ask “How old were you when you first started having panic attacks?” Similarly, if a patient meets diagnostic criteria for alcohol dependence, the interviewer is then prompted to ask “How old were you when you first started having these alcohol use problems?” By directly comparing the ages of onset these SCID questions elicited, we categorized all patients into one of three groups: 1) anxiety problem preceded alcohol problem; 2) alcohol problem preceded anxiety problem; or, 3) anxiety and alcohol problems started simultaneously. (Note that where multiple anxiety disorders were present, we used the one with the earliest age of onset to categorize the patient.)

As elaborated in the “Discussion” section, the reader should note that this method did not confirm that individuals met full diagnostic criteria (vs. a subclinical prodromal state) at the time of the identified age of onset.

SCID: Modifications/Additions
In addition to psychiatric diagnoses, the SCID interview was expanded slightly to accommodate our particular study needs including documentation of 1) the periods of remission of a duration of at least three contiguous months and the timing of relapses related to specific periods of remission; 2) alcohol withdrawal symptoms and dependence severity (according to DSM-IV rules and guidelines) in which respondents were instructed to endorse only withdrawal symptoms that occurred exclusively or worsened dramatically within one to three days of abstinence (to more clearly distinguish withdrawal symptoms from anxiety symptoms); and 3) ages at which various alcohol use–related milestones were reached such as first experience of withdrawal symptoms, first intoxication, first regular intoxication, and so forth. Finally, because these survey items were not a part of the standard SCID, their psychometric qualities cannot be judged on the basis of those of the interview. We used them, nonetheless, because they allowed us to obtain information of interest in a systematic way where psychometrically established instruments for obtaining the same information were not available.

Time-Line Follow-Back
The time-line follow-back (TLFB) interview (Sobell and Sobell, 1995) was used as a method of estimating the daily quantity and frequency of alcohol use over the four months preceding the baseline interview and the time between subsequent assessments. Using a calendar, the respondent provides retrospective estimates of daily drinking over a specified amount of time. Several memory aids can be used to enhance recall (e.g., holidays, important weekends). The TLFB interview has been shown to have good psychometric qualities in both clinical and nonclinical populations (Sobell and Sobell, 1995).

Interviewer Training in Inter-rater Reliability
Four advanced psychology student research assistants served as interviewers for the study. Interviewer training took place over a 4-week period and entailed attending didactic and video presentations (on the SCID and TLFB interviews), observing a licensed psychologist model these interviews and role-playing these interviews with corrective feedback. Inter-rater reliability was assessed in the following manner: All baseline and follow-up interviews were tape-recorded. Twenty of these interviews (five for each interviewer) were then randomly selected and evaluated by a different interviewer. This second interviewer completed SCID modules based on the taped interview, and we compared these diagnostic decisions with those of the original interviewer. There was 100% inter-rater agreement on diagnoses.

Procedure
Screening. Within three days of admission to the treatment facility, individuals who were assigned to the residential intensive substance abuse treatment program were given a brief initial screening form for the purposes of the present study. This form asked respondents about recent substance use–related problems and anxiety symptoms. Approximately one week after admission, seemingly eligible individuals who expressed an interest in participating in the study were invited for a final screening visit in which the trained interviewer administered the alcohol dependence module of the SCID, along with a SCID-based screen for the presence of psychotic symptoms and mania.

Baseline Assessment. Those individuals meeting full eligibility criteria and given informed consent (see above) were then asked to complete a questionnaire packet. The interviewer subsequently administered the TLFB interview and SCID-IV anxiety disorder and major depression modules. All SCID-IV modules and TLFB were keyed to the four months preceding admission.

Follow-up Assessment. Ninety days after the baseline assessment, the research coordinator began the process of contacting a participant for the follow-up assessment. When necessary, the “contact person” (identified by the patient during the baseline assessment) was called to help locate the patient. On contact, a participant was offered several possible dates to return to the treatment facility for this assessment. We required that the session take place between 90 and 120 days after the baseline assessment. This follow-up assessment consisted of a questionnaire packet, the TLFB interview (covering the period from the baseline assessment to the follow-up assessment), and the same SCID-IV modules that were administered during the baseline assessment; however, this time participants were instructed to reference responses to the past 30 days. (Note that we focused on the past 30 days to provide a clear temporal distinction between the baseline and follow-up interviews.) In rare circumstances (i.e., four cases), a participant who was unwilling or unable to return to the treatment facility was asked to complete the questionnaire packet by mail and the interview by phone. Participants were paid a total of $95 if they completed both the baseline and follow-up assessments.

Statistical Analysis
Analyses include $\chi^2$ and $t$ tests to examine differences between the anxiety and no-anxiety groups at the baseline and follow-up assessments. Where appropriate, group by time (i.e., from the baseline to the follow-up assessment) interactions are examined. Survival analyses are used to contrast the groups on time to various relapse milestones. For these survival analyses, 120 days was used as the interval for right-censored data; however, in those cases where no relapse had occurred by the time of the follow-up interview, the time interval was set as the number of days between the baseline and follow-up assessments (never less than 105 days). Finally, logistic regression analyses were used to examine the capacity of specific baseline anxiety diagnoses to predict alcohol and anxiety outcomes at the follow-up assessment. Note here that we were unable to represent agoraphobia without panic and OCD in the logistic regression analyses because they occurred in only one and two individuals, respectively.

The available statistical power for the study is keyed to the primary prediction contrasting those with, versus without, a baseline anxiety disorder in terms of their follow-up alcohol use status. Analyses involving comparisons of subgroups (e.g., those whose anxiety disorder persisted over the follow-up versus those whose anxiety disorder remitted by the follow-up) represent exploratory analyses and have adequate power to show significance for only relatively large effect sizes. Along the same lines, statistical power was greatest for analyses that lumped those with any baseline anxiety disorder into a single category (i.e., “anxiety disorders”). However, we also used regression analysis techniques allowing us to study the influence of specific anxiety syndromes on alcohol outcomes, albeit, again, with less statistical power.

RESULTS
Comparison of Follow-up Completers to Noncompleters
Those lost to follow-up ($n = 29$) were compared with those retained ($n = 53$) on a variety of baseline measures including...
demographics, alcohol use, and age at which participants first used alcohol, first became intoxicated, regularly consumed alcohol, began problem drinking, and reached their heaviest drinking level. No significant differences between follow-up completers and noncompleters were found on these variables. We also examined rates of anxiety and depression diagnoses, withdrawal symptoms, and use of antidepressant or anxiolytic medications at baseline between follow-up completers and noncompleters. Few significant differences emerged. However, we did find that those who were retained at the follow-up had significantly greater alcohol withdrawal symptoms at the baseline (7.4 vs. 6.0; $F(1,81) = 4.84, p < 0.031$) than did those not retained at the follow-up. These data show that those not retained at the follow-up did not differ from those who were retained at the follow-up on baseline variables relating to the primary study predictions.

### Comparisons of Those With and Without Baseline Anxiety Disorder

Twenty-nine of the 53 cases with follow-up data (i.e., 55%) had at least one anxiety disorder at the baseline assessment. Table 1 compares those with a baseline anxiety disorder with those without a baseline anxiety disorder on variables related to demographics, anxiety/depression indicators, and alcohol use/abuse history/outcomes.

**Demographics.** As shown in Table 1, there was no significant difference between the groups in participants’ age at the time of the baseline assessment; however, the anxiety-disordered group was slightly more than twice as likely to be female ($p = 0.05$). Depression was also significantly more likely at baseline and follow-up among individuals with a baseline anxiety disorder ($p < 0.05$). Also shown in Table 1 is the high percentage of comorbid patients who reported that the onset of their anxiety disorder symptoms began before the onset of their drinking problems. However, those who were retained at the follow-up did not differ from those who were retained at the follow-up. These data show that those not retained at the follow-up did not differ from those who were retained at the follow-up on baseline variables relating to the primary study predictions.

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Alcohol Variables at Baseline and Follow-up. As Table 1 shows, the groups did not differ in terms of the age at which individuals reached important alcohol disorder milestones; however, alcohol withdrawal symptoms at the baseline assessment were more pronounced among those with a baseline anxiety disorder ($F(1,51) = 5.23, p < 0.05$). Although subjects in the two groups did not differ in terms of the number of drinks they were consuming in the month leading up to the study, those with a baseline anxiety disorder were drinking significantly more in the month preceding the follow-up assessment as compared with those with no baseline anxiety disorder ($F(1,51) = 8.89, p < 0.004$). Consistent with study predictions, a significant group by time interaction ($F(1,51) = 4.38, p < 0.05$) confirms that those with no baseline anxiety disorder showed a greater reduction in the amount of their drinking over the course of the follow-up than was true for those with a baseline anxiety disorder. Also consistent with study predictions, a higher percentage of those with an anxiety disorder returned to drinking (of any amount) and had had at least one drinking binge (i.e., four standard drinks for women and five for men in a single drinking episode) over the course of the follow-up compared with those in the nonanxiety disordered group ($\chi^2 = 5.33, p < 0.05$ and $\chi^2 = 5.85, p < 0.05$, respectively) (Table 1). The percentage of those who drank on at least three consecutive days over the course of the follow-up was, as predicted, greater in the anxiety-disordered group, but this effect was not significant ($\chi^2 = 2.93, p = 0.087$). Similarly, although the absolute difference in the rate of alcohol dependence between the groups at the follow-up assessment was in the predicted direction, the difference was not significant.

Time to Relapse. Survival analyses (Kaplan-Meier) were used to contrast the time to relapse between those with versus without a baseline anxiety disorder. Separate analyses were conducted for various relapse criteria including the first occurrence of any drinking, a drinking binge, and three consecutive days of drinking. Results shown in Fig. 1 indicate that there were fewer days to first drink among those with, versus those without, an anxiety disorder (log rank $= 5.69, p < 0.05$). Similarly, the days to first drinking binge were significantly fewer in the anxiety disorder group (log rank $= 5.83, p < 0.05$). However, the number of days to the first instance of three consecutive days of drinking, although showing a trend in the predicted direction, did not reach conventional criteria for statistical significance (i.e., $p < 0.05$).

Relationship of Specific Anxiety Disorders to Alcohol Outcomes

To determine the relative capacity to predict alcohol outcomes of specific baseline anxiety disorders, baseline depressive disorder, and multiple baseline anxiety disorders (i.e., those with more than one baseline anxiety diagnosis, “multianx”), we used a forward stepwise (conditional) logistic regression model. Using any alcohol use over the follow-up as the outcome, only social phobia accounted for sufficient predictive variance to enter the equation ($p <$
Depression at the baseline and follow-up assessments. All diagnoses shown in Fig. 2, except GAD and depression, were significantly more likely to be identified at the follow-up assessment when present at baseline assessment (Fisher’s exact tests: all \( p < 0.05 \)). To evaluate the capacity to predict anxiety disorder at the follow-up assessment (i.e., anxiety persistence) using baseline variables, we again used forward stepwise (conditional) logistic regression analysis. Predictors included specific baseline anxiety disorders, baseline multianx, order-of-onset for comorbid disorders, and baseline depression. The final model included only two variables, multianx \(( p < 0.01, \text{OR} = 21.31, 95\% \, CI = 2.56 \text{ to } 177.32)\) and depression \(( p = 0.06, \text{OR} = 13.08, \text{CI} = 0.90 \text{ to } 191.08)\). That is, individuals with multiple anxiety disorders or depression at the baseline were at the greatest risk for having at least one anxiety disorder at the follow-up; however, depression only approached statistical significance in the model \(( p = 0.06)\). Knowing whether an individual had any particular anxiety disorder, or the order-of-onset for the comorbid disorders, did not add additional predictive information.

### Cross-Sectional Relationship of Anxiety Persistence and Alcohol Disorder Relapse at the Follow-up Assessment

The prospective association between anxiety disorder persistence and alcohol disorder relapse is of obvious theoretical and practical interest. Does relapse to pathologic alcohol use after treatment contribute to the persistence of comorbid anxiety disorder? Alternatively, does persistent anxiety disorder contribute to drinking relapse after alcoholism treatment? Unfortunately, the prospective relationships implied in these and related questions cannot be formally assessed in the present dataset because the status of individuals on both variables is not known until the follow-up assessment. Therefore, we can only examine this relationship at the follow-up assessment, which limits us to a cross-sectional approach.

As shown in Table 2, somewhat less than one-third of cases (31%) with a baseline anxiety disorder continued to have an anxiety disorder through to the follow-up in the absence of relapse to alcohol dependence. This can be contrasted to the relatively low rate (i.e., 3.4%) at which those who had a baseline anxiety disorder relapsed to alcohol dependence in the absence of a persistent anxiety disorder. This shows that the chance that a baseline anxiety disorder, or the order-of-onset for the comorbid disorders, did not add additional predictive information.

**Prospective Associations.** Of the 29 individuals who met diagnostic criteria for at least one anxiety diagnosis at the baseline assessment, 15 individuals (approximately 52%) no longer met criteria for any anxiety disorder by the follow-up assessment. All diagnoses shown in Fig. 2, except GAD and depression, were significantly more likely to be identified at the follow-up assessment when present at baseline assessment (Fisher’s exact tests: all \( p < 0.05 \)). To evaluate the capacity to predict anxiety disorder at the follow-up assessment (i.e., anxiety persistence) using baseline variables, we again used forward stepwise (conditional) logistic regression analysis. Predictors included specific baseline anxiety disorders, baseline multianx, order-of-onset for comorbid disorders, and baseline depression. The final model included only two variables, multianx \(( p < 0.01, \text{OR} = 21.31, 95\% \, CI = 2.56 \text{ to } 177.32)\) and depression \(( p = 0.06, \text{OR} = 13.08, \text{CI} = 0.90 \text{ to } 191.08)\). That is, individuals with multiple anxiety disorders or depression at the baseline were at the greatest risk for having at least one anxiety disorder at the follow-up; however, depression only approached statistical significance in the model \(( p = 0.06)\). Knowing whether an individual had any particular anxiety disorder, or the order-of-onset for the comorbid disorders, did not add additional predictive information.

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1. These large confidence intervals reflect the relatively strong associations of multianx and depression with anxiety persistence \(( n = 0.593 \text{ and } 0.384, \text{respectively})\) in combination with the low number of subjects eligible for this analysis (i.e., restricted to only those with a baseline anxiety diagnosis \( n = 29)\). Further restricting the sample eligible for this analysis, the mechanics of the logistic regression were not tolerant of the single case category so we had to censor the one individual who reported a simultaneous onset of alcohol dependence and anxiety disorder (i.e., as related to the order-of-onset predictor variable) \(( \text{resulting, } n = 28)\). Although the significance levels \((p-values)\) are as shown, the reader is cautioned that the odds ratio estimates are imprecise, as the large confidence intervals suggest.
disorder will persist in the absence of a relapse to alcohol dependence is approximately 10 times greater than the chance that a relapse to alcohol dependence will occur when a baseline anxiety disorder does not persist (effect size, $r = 0.36$). Unfortunately, such low cell sizes (e.g., only one case in the cell representing a relapse to alcohol dependence among those whose baseline anxiety disorder did not persist) violate assumptions associated with $\chi^2$ analysis. A statistic that is appropriate under these circumstances, Fisher’s exact test, shows the probability that this distribution is due to chance to be low ($p = 0.08$); however, it is not sufficiently low (i.e., $p < 0.05$) to reject the null hypothesis unambiguously.

**DISCUSSION**

A baseline assessment occurring shortly after patients entered an alcoholism treatment program showed that approximately half of the study sample met criteria for at least one of the anxiety disorders assessed. Consistent with this, Kushner et al. (1990) found that the median rate of anxiety disorder in studies of alcoholism treatment patients was about 44%. Although finding a substantial rate of anxiety disorder in alcoholism treatment patients may be highly replicable, the practical and theoretical implication of comorbidity remains speculative and even controversial (Kushner et al., 2000a; Schuckit and Hesslbrock, 1994). The present study provides data that further illuminate issues related to this association.

**Baseline Anxiety Disorder and Risk for Relapse to Drinking**

Patients with an active anxiety disorder at the onset of alcoholism treatment (i.e., at the baseline assessment) were at a significantly greater risk for relapse to drinking by the follow-up assessment than were those with no baseline anxiety disorder. This finding held true across a number of diverse outcome measures including any alcohol use, absolute amount of alcohol use (Table 1), and time to the first instance of several relapse markers (Fig. 1). Only the rate of active alcohol dependence at the follow-up and the rate of (and time to) alcohol consumption on three consecutive days during the follow-up period failed to differentiate the groups significantly; however, group effects for these outcomes were sizable (i.e., medium) and in the predicted direction (Table 1 and Fig. 1). These findings add to a growing list of studies showing that various types of psychopathology can worsen alcoholism treatment outcomes (Labouaty et al., 1992; Rounsaville et al., 1987; Tomasson and Vaglum, 1996) and directly replicate findings reported by Driessen et al. (2001).

We also investigated whether specific anxiety disorders, multiple anxiety disorders, or depression were especially predictive of drinking relapse. Interestingly, we found that although panic disorder was the most predictive of a relapse to alcohol dependence, social phobia was the most predictive of a relapse to any drinking. Interpreted at face value, these findings suggest that panic disorder confers a greater risk than do other anxiety disorders for a major relapse (i.e., that meeting criteria for alcohol dependence), whereas social phobia confers a greater risk than do other anxiety disorder for a minor relapse (i.e., that including drinking but not meeting criteria for alcohol dependence). However, this conclusion fails to take into account the possibility that some with social phobia might redevelop alcohol dependence past our follow-up window. Nonetheless, these findings do suggest that panic disorder and social phobia present a greater risk for a drinking-related relapse within 4 months of treatment than do other anxiety disorders. This may help to explain why panic disorder and social phobia are the most common anxiety disorders found in this and several other studies of comorbidity in alcoholism treatment patients (c.f., Kushner et al., 1990).

**Anxiety Disorder Persistence**

**Substance-Induced Versus Independent Anxiety Disorder.** Approximately 31% with a baseline anxiety disorder had a follow-up anxiety disorder in the absence of relapse to pathologic alcohol use (defined as alcohol dependence$^2$) (Table 2). This translates to 17% of the total follow-up sample, which can serve as a lower-limit estimate of the rate of independent anxiety disorder in our sample. It is a lower-limit estimate because this finding does not speak to whether or not persistent anxiety was dependent on pathologic alcohol use in cases where relapse did occur; that is, there is no logical reason why alcohol relapse could not occur in either case. Further qualifying this estimate as conservative is the uncontrolled possibility that anxiety disorders that resolved in the absence of relapse to alcohol disorder might still have been independent.  

$^2$Because pathological alcohol use that includes withdrawal is thought to contribute to alcohol-induced DSM-IV anxiety syndromes, we concluded that alcohol dependence was the best relapse criterion for the purpose of exploring this issue. This is consistent with numerous studies suggesting that alcohol dependence, versus use/abuse in the absence of dependence, is the most consistently related to comorbid anxiety disorder (c.f., Kushner et al., 2000a).

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**Table 2. Cross-Tabulations of Anxiety Persistence with Relapse to Alcohol Dependence†**

<table>
<thead>
<tr>
<th>Alcohol dependence</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistent anxiety</td>
<td>5 cases</td>
<td>9 cases</td>
</tr>
<tr>
<td>R% - 35.8</td>
<td>R% - 64.2</td>
<td></td>
</tr>
<tr>
<td>C% - 83.3</td>
<td>C% - 39.1</td>
<td></td>
</tr>
<tr>
<td>n% - 17.2</td>
<td>n% - 31.0</td>
<td></td>
</tr>
<tr>
<td>N% - 9.4</td>
<td>N% - 17.0</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1 case</td>
<td>14 cases</td>
</tr>
<tr>
<td>R% - 6.7</td>
<td>R% - 93.3</td>
<td></td>
</tr>
<tr>
<td>C% - 17.7</td>
<td>C% - 60.9</td>
<td></td>
</tr>
<tr>
<td>n% - 3.4</td>
<td>n% - 48.3</td>
<td></td>
</tr>
<tr>
<td>N% - 1.8</td>
<td>N% - 26.4</td>
<td></td>
</tr>
</tbody>
</table>

R% percent in row; C% percent in column; n% percent of all those with a BL anxiety disorder, n = 29; N% percent of all those in the follow-up sample, n = 53. † $p < 0.10$. 

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dependent from pathologic alcohol use (e.g., perhaps anxiety nonpersistence was due to anxiolytic therapy or chance timing in the natural course of the anxiety disorder). In short, although we can assert with reasonable confidence that 17% of our total follow-up sample had an anxiety disorder that was independent from ongoing pathologic alcohol use, we cannot rule in or out the possibility that this was also true for a higher percentage of cases. In fact, it seems likely that a higher percentage of cases had an independent anxiety disorder, based on the work of Grant et al. (2004). Using strictly applied DSM-IV criteria, they found that 33% of individuals who underwent alcoholism treatment in the 12 months preceding their study had an independent anxiety disorder over that same time period.

Order of Comorbid Disorder Onset. It is also noteworthy that the order of comorbid disorder onset, sometimes used to segregate comorbid cases in terms of their need for specific psychiatric attention (e.g., Allan, 1995), did not emerge as a significant predictor of anxiety disorder persistence in the logistic regression model. Consistent with this are studies showing that comorbid depression, whether starting before or after the emergence of regular pathologic drinking, marks a poor prognosis after substance abuse treatment relative to those with no depression (Carroll et al., 1993; Hasin et al., 1996; Kadden et al., 1995; Rounsaville et al., 1986). Also consistent with this finding are studies showing that depression symptoms respond equally well to antidepressant treatment regardless of whether they started before or after substance abuse (Gawin et al., 1989; Gianninni et al., 1986; Nunes et al., 1998; Schuckit, 1985; Ziedonis et al., 1991).

Such data, along with substantial inconsistencies between studies in how comorbid disorder onsets are dated (e.g., Kushner et al., 1990), highlight problems associated with reliance on the order-of-disorder-onset criterion for making clinical decisions. In the present study, for example, our method relied on the identification of the age at which the patient first experienced “problems” or symptoms associated with each diagnosis identified by the SCID. Therefore, it is not certain that the individual met full diagnostic criteria (vs. a subdiagnostic prodromal state) for a given disorder at the time of its identified onset. Dating the onset of disorders using a different method (e.g., earliest age at which all diagnostic criteria for a disorder are met) would, no doubt, produce a somewhat different distribution of patients across our three order-of-disorder-onset categories. These reconfigured categories, in turn, might account for more (or less) predictive variance associated with anxiety persistence than did ours.

Further, to the extent that the goal of dating the onset of comorbid disorders is to distinguish an “independent” from a “substance-induced” anxiety disorder, it makes sense to also consider the clinical status of the anxiety disorder during any periods of protracted abstinence from alcohol use (i.e., Grant et al., 2004). For example, a comorbid anxiety disorder that persists over a significant period of alcohol abstinence, regardless of the order of comorbid disorder onset, could be considered as comparable to cases in which an anxiety disorder onset preceded that of a comorbid alcohol disorder. How well these (and other) possible modifications of subclassifying comorbid cases would prospectively predict disorder trajectories remains in question. Codifying a single operational protocol and set of definitions for subclassifying comorbid cases based on the inter-related course of the disorders remains a critical prerequisite to moving this agenda forward. The work of Grant and colleagues (2004) strikes us as an excellent step in this direction.

Prospective Relationship of Anxiety Persistence to Alcohol Relapse. Does relapse to drinking lead to anxiety persistence or, possibly, vice versa? This seemingly straightforward and obviously important question is deceptive in its complexities and, unfortunately, cannot be addressed prospectively in the present data. This is because we cannot assess the capacity of a particular outcome variable (e.g., persistence of anxiety disorder) to prospectively predict another outcome variable (e.g., alcoholism treatment outcome). To accomplish this, we would require, minimally, one additional wave of postbaseline data collection, which, again, unfortunately, we do not have. Further, as discussed below, controlled treatment studies could shed important new light on the causal associations between anxiety disorder and alcohol relapse.

Specific Anxiety Syndromes. Not surprisingly, having any particular anxiety disorder at baseline was generally a significant predictor of having that same anxiety disorder at the follow-up. However, this association did not hold for GAD, which was rather common at the baseline (approximately 21%) but relatively rare at the follow-up (about 6%). Similarly, depression was extremely common at the baseline (approximately 60%) but relatively rare at the follow-up (approximately 15%) (Fig. 2). Because GAD and depression were, relative to the other disorders assessed, especially likely to be transitory in the months after alcoholism treatment, it might be that these disorders are more likely than the other disorders assessed to be secondary to pathologic alcohol use/withdrawal per se or to the myriad stresses and difficult adjustments (e.g., legal, financial, family) that can be associated with events leading up to the initiation of alcoholism treatment.

Importantly, the presence of multiple anxiety disorders in a little more than half of those with any baseline anxiety disorder potentially complicates the interpretation of anxiety persistence data. Therefore, we examined persistence through regression analysis in which shared and unique variation associated with specific predictors can be partitioned. This approach showed that having multiple anxiety disorders at baseline, rather than any particular baseline anxiety disorder, was a significant predictor of anxiety disorder persistence at the follow-up. We understand this
finding to suggest that anxiety disorder persistence is, in some significant part, a function of the increased psychiatric severity for which the presence of multiple anxiety disorders, relative to a lone anxiety disorder, is a marker. Also consistent with this interpretation, the only other predictor accounting for enough unique variance to enter the equation predicting anxiety persistence was a baseline depression diagnosis. In short, although specific anxiety disorders (i.e., panic disorder and social phobia) predict alcohol relapse (above), psychiatric severity (as indexed by the presence of multiple anxiety disorders and depression) predicts anxiety disorder persistence.

**Future Work**

*Treatment of Comorbid Anxiety Disorders.* As mentioned above, observational studies that use multiple follow-up assessments would offer significant opportunities for improving our understanding of the prospective covariation of comorbid disorders. However, treatment studies are especially well suited to further clarify the causal influence(s) that may exist between comorbid disorders. Random assignment in experimental clinical trials would, for example, avoid self-selection issues (e.g., based on anxiety severity) that can confound causal conclusions in purely observational studies. On clinical grounds, establishing interventions that can improve anxiety and alcohol outcomes in comorbid patients is obviously valuable.

In the context of comorbidity, however, it is useful to consider separately the impact of specific anxiety treatment on anxiety outcomes versus alcohol outcomes. For example, it cannot be taken for granted that standard anxiety disorder treatments, developed for and validated in psychiatric outpatients, will be effective when applied to comorbid patients. More than a pedantic point about the need for prudence in generalization, there is a very real possibility that anxiety disorders that are comorbid with alcohol use disorder require unique treatment approaches (see Kushner et al., 2000a). Consistent with this, Randall et al., (2001) and Bowen et al., (2000) failed to find treatment effects for standard cognitive-behavioral therapies for social phobia and panic disorder (respectively) when applied to comorbid patients. Note, however, the evidence for the effectiveness of standard anxiety treatments in comorbidity is mixed (c.f., Kushner et al., 2000a).

As a distinct matter, it is important to consider that unless comorbid anxiety disorder treatment is effective, the prediction that such treatment would result in improved alcohol outcomes (i.e., based on the hypothesis that the symptoms of comorbid anxiety disorder can be a cause of relapse) is not tested validly. In fact, the small number of studies that have been successful in treating comorbid anxiety disorder have generally resulted in better alcoholism treatment outcomes (e.g., Fals-Stewart and Schafer, 1992; Kranzler et al., 1994; Tollefson et al., 1992). An implication of this is that efforts aimed at reducing drinking relapse by treating comorbid anxiety disorder must be done hand-in-hand with research into what constitutes effective treatment for comorbid anxiety disorder.

**Gender.** We found significantly more women among those with a baseline anxiety disorder than among those with no baseline anxiety disorder (Table 1). This is not surprising, given that a greater proportion of women than men have anxiety disorders in the general US community (e.g., Lewis et al., 1996) and among alcohol-disordered individuals (e.g., Kushner and Sher, 1993; Mann et al., 2004). This is not to say that the association between gender and anxiety disorder is especially strong among individuals with alcohol use disorders. In fact, Kushner and Sher (1993) found that gender did not interact with alcohol disorder status in predicting the cross-sectional presence of a comorbid anxiety disorder; for example, the proportional difference in risk for anxiety disorder between men and women was the same among those with an alcohol use disorder as among those without an alcohol use disorder. However, this still does not clarify whether gender status moderates the association between anxiety disorder and alcohol use disorder outcomes. This question is left to other work, as our study was too small to allow for the examination of these interaction effects.

Notably, the need for future work that examines gender effects in comorbidity seems to be highlighted more than alleviated by the existing work. Lewis et al. (1996) and Greenfield et al. (1998) present findings suggesting that gender and comorbid psychiatric anxiety/depressive disorders have independent but not interactive effects on drinking outcomes. Mann et al. (2004) reported, on the other hand, that comorbid anxiety/depressive disorders do not affect alcohol outcomes in men and actually improve these outcomes in women. However, Tomasson and Vaglum (1996) reported that comorbid panic attacks worsen alcohol outcomes in men but do not affect them in women. Some studies also point to gender differences in the etiology of comorbid associations. For example, Sonne, et al. (2003) reported that PTSD precedes the onset of comorbid alcohol disorder more often in women than in men. Further, several studies from our lab suggest that men and women show differences in the way several psychological characteristics (e.g., tension-reduction alcohol outcome expectancies) affect the association between anxiety and drinking (e.g., Abrams and Kushner, 2004; Kushner et al., 2000b; Kushner et al., 1994). Clearly, the effects of gender on the development and impact of comorbidity are ripe for additional research.

**Study Limitations**

**Sample Size.** Sample sizes, especially for analyses related to specific anxiety disorders and anxiety persistence, are relatively small in this study. For example, the effect linking anxiety persistence to alcohol dependence, although me-
dium in size ($r = 0.36$) and, arguably, clinically meaningful in distribution (Table 2), is not statistically significant ($p = 0.08$). Further, the low number of cases of baseline OCD and agoraphobia without panic precluded analyzing the predictive value of these disorders in logistic regression analyses. Unfortunately, it is not clear what, if anything, low rates for these two anxiety disorders suggest. For example, the rate of current OCD in our sample (approximately 2%) is between the one-month (1.3%) and lifetime rates (2.5%) for OCD reported in the Epidemiologic Catchment Area survey (Regier et al. 1990); however, those data do not clarify how the rate of OCD is changed by the presence of an alcohol disorder. Similarly, that report did not segregate agoraphobia with versus without panic attacks. Kushner et al. (1990) reported the range of lifetime OCD in published studies of alcoholism treatment patients to be from 2.7% to 12%. We are not aware of any studies reporting the rate of agoraphobia without panic attacks in alcohol-disordered patients (approximately 4% in our sample). Finally, it is also important to consider that the primary analyses comparing subjects with versus without anxiety disorders (cell sizes of greater than 20) were least affected by the limited sample size.

Recruitment and Retention. Of the thousand-plus patients who cycled through the chemical dependency treatment evaluation process during the one-year recruitment period, approximately 40% returned a letter of interest and were deemed as “probably eligible” to participate. As noted in the “Methods” section, the majority of loss here was passive in nature (i.e., did not return the letter of interest), leaving unanswered questions as to these individuals’ clinical status or reasons for not returning the letter. Although we mentioned in the recruitment letter that nonanxious control subjects are also needed for participation, it is possible that the title and description of the study was more interesting to those with anxiety problems. If this were the case, it could mean that anxiety disorder rates were inflated in the study relative to the entire population from which we sampled. Arguing against this conclusion, however, is our earlier observation that the anxiety disorder rates we found were just slightly over the median rate found in a number of earlier studies (as reviewed by Kushner et al., 1990). In any case, our study was not designed to estimate anxiety disorder rates among alcoholism treatment patients as much as it was to assess the impact of comorbid anxiety disorder on relapse risk. Regarding this primary aim, we have no reason to believe this initial step introduced significant bias.

Other junctures in the recruitment process also warrant consideration. Approximately 35% of individuals indicating an interest in participating were not invited for a formal screening due to limitations in staffing. Since these losses were unrelated to any characteristics of the potential subjects, they should not have introduced any bias into the sample. Also, approximately 30% of those we did invite to the formal evaluation did not respond. For this group, as with those who failed to respond to the initial letter describing the study (above), we cannot rule out the possibility that some systematic bias was operative. Again, there might have been less interest (and hence greater loss) among those not having anxiety problems. As noted above, such bias could serve to raise the rate of anxiety disorder identified in our sample relative to the entire population but would not bias our tests of study hypotheses. Beyond this conjecture, we cannot know why these individuals failed to participate and so cannot rule out other possible selection biases being introduced at this recruitment step.

Finally, it should be noted that our retention rate over the follow-up (65%) was low compared with some published retention rates in alcoholic patients of 80% or higher (e.g., LaBounty et al., 1992). We believe this resulted, in part, from our having recruited exclusively from among patients entering an “intensive” residential alcoholism treatment program. These patients, by hospital protocol, were more severely disordered and often without a stable residence compared with patients triaged to any of the several lower intensity treatment options offered by the service. In addition to challenges posed by locating subjects without a permanent address, we speculate that the payment schedule and amounts used in this study were not optimally conducive to retention. For example, a comparable study we currently have ongoing has met with greater recruitment success and retention by paying subjects more for participating and by providing the bulk of the payment only after the follow-up assessment is completed. Finally, it is important to note that we believe that attrition over the follow-up was not systematically related to key study variables as contrasts between those who did and did not provide follow-up data on these variables did not reveal significant differences.

Uncontrolled Anxiety Treatments. Another feature of our study that should be considered when interpreting the results is the lack of control over presumptive anxiety treatments that subjects may have received before the baseline assessment or over the follow-up period. In fact, many subjects in both the anxiety disordered and nonanxiety disordered groups were taking psychopharmacological medications commonly used for the treatment of anxiety disorder (e.g., selective serotonin reuptake inhibitors). As alluded to earlier, subgroup membership in an observational study such as ours, including whether psychiatric medications are being used, is not based on random assignment and may well reflect a self-selection process (e.g., based on clinical severity). Therefore, we cannot know with any certainty what impact the use of psychiatric medications had on the findings of this study. With that said, it is notable that despite routinely accessing pharmacological therapies commonly used in the treatment of anxiety disorder, ongoing anxiety disorder remained fairly common.
throughout the study. This observation could reflect a reduced efficacy for standard anxiety treatments among co-morbid patients (see earlier discussion of this possibility) or could suggest that many of these patients were not being optimally treated (e.g., in terms of dose). In any case, it seems reasonable to surmise that anxiety disorder rates and anxiety persistence would be even greater in the absence of this medication use.

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