REGULAR ARTICLES

The Effects of Major Depression on Alcoholism

Five-Year Course

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Some patients come into treatment with clear cases of both major depression (MDD) and alcoholism. Although assumptions are often made about the relationships of these two conditions, little empirical information exists on the effects of changes in MDD on the course of alcoholism in patients presenting at psychiatric facilities. The authors used survival analysis with time-dependent covariates to investigate the effects of remissions and relapses of MDD on the 5-year course of alcoholism in 127 dual diagnosis patients. Changes in the status of MDD had strong, significant effects on the course of alcoholism. Improvement in MDD status increased the chances of remission in alcoholism and reduced the chances of alcoholism relapse. The status of MDD appears to have an effect on the course of alcoholism in patients with severe affective disorders. (American Journal on Addictions 1996; 5.144-155)

Despite increasing attention to "dual diagnosis" psychiatric patients, surprisingly few empirical studies have investigated the course of alcoholism among patients treated at psychiatric facilities who present with both alcoholism and major affective disorders.' Although a large literature has focused on the distribution and meaning of depression among patients treated at alcoholism or drug facilities, the applicability of this literature to the psychiatric patient is uncertain, and the alcohol problems of psychiatric patients with serious affective disorders remain relatively unresearched.

Previously, we showed that many patients in treatment for serious affective disorders have comorbid alcohol problems.[1]

These alcohol problems were likely to remit for at least 6 months during a 5-year follow-up period, although many patients with remissions subsequently relapsed.[2,3] In research aimed at explaining these results, we investigated the effects of numerous demographic characteristics and the status of clinical variables at study intake on the outcome of the patients' alcoholism. The factors found to be significantly related to alcoholism remission in this previous research included subtype of affective disorder at intake (schizoaffective patients had worse outcome; bipolar patients had better outcome), previous duration of alcoholism (longer duration predicted worse outcome), and alcohol dependence severity[4] (greater severity predicted worse outcome).

Although several conditions are often assumed to be related to the outcome of alcoholism in patients like those we studied, some of these assumptions were not supported by our empirical work. Several of the variables that were not significantly related to alcoholism remission among these patients were the primary/secondary distinction (identified by order of onset), antisocial personality disorder (ASPD), bipolar I disorder, and demographic characteristics, including sex and age. Also, none of the variables we studied significantly predicted relapse of alcoholism, despite the clinical importance of understanding factors contributing to relapse.

Characteristics or conditions of patients at treatment entry may be important predictors of the course of a disorder. However, many factors can change over time, especially if the follow-up period is prolonged. In studying the course of alcoholism in these dual diagnosis patients, an obvious area of further investigation during follow-up was the clinical status of major depression (MDD). Thus, we investigated whether improvement in MDD increased the chances of a remission in alcoholism, and also whether changes in the clinical status of MDD affected the likelihood of subsequent relapses in alcoholism.

METHODS

Subjects

Subjects were psychiatric patients in the clinical studies portion of the NIMH Collaborative Depression Study. The general methods of the study have been described elsewhere.[5] Subjects for the Collaborative Study were recruited from medical school treatment facilities in Boston, Chicago, Iowa, New York, and St. Louis, between 1978 and 1981. Patients were included if they received a diagnosis of a unipolar or bipolar major affective disorder or schizoaffective disorder according to the Research Diagnostic Criteria (RDC),[6] as evaluated by the Schedule for Affective Disorders and Schizophrenia (SADS)[7]. Of the 955 subjects, 135 also received a diagnosis of current alcoholism at intake into the study. This diagnosis was the inclusion criterion for the present study. Of these 135 patients, 127 (94%) participated in follow-up. These 127 patients constituted the sample for previous reports on the course of alcoholism in patients with affective disorders[2,3] as well for this report.

All 127 patients were white, 40% were female, 31% were married, and 24% had never been married. About two-thirds were under 40 years of age. About one-quarter of the patients were from Iowa, another one-quarter from Boston, a third from St. Louis, and the rest were from New York and Chicago. At intake into the study, 88% were psychiatric inpatients, and the remainder were outpatients. The affective disorders were severe and were required to be non-organic by the RDC criteria. Although the minimum duration of affective disorders for RDC was 2 weeks, most of these patients who came into tertiary treatment facilities had been severely depressed

for considerably longer. The following affective diagnoses were received by these patients: 5% schizoaffective disorder, 13% bipolar I, 8% bipolar II, and 74% unipolar MDD.[2] All gave informed consent to participate.

As noted earlier,[3] the range in severity of alcoholism (number of RDC alcoholism symptoms) of these patients was approximately the same as in a sample of alcoholism rehabilitation patients assessed with the same interview. However, mean severity was lower in the Collaborative patients because of a more even spread across severity levels in the present sample than in the alcoholism rehabilitation patients.

Of the 127 patients, 97 were followed for 5 full years. Ten patients died before the end of the follow-up (5 suicides, 2 cancer, 3 other alcohol-related causes), and the remainder were lost to follow-up or refused participation before the end of the study. Data were included on all patients up to the time that they died or were lost to follow-up because we used a method of statistical analysis, survival analysis, that is specifically designed to use all available data on subjects, even those who died or dropped out before the end of the study period (see description of analyses, below). As reported earlier, the cumulative probability of remission from RDC alcoholism was 0.90 after 5 years, and the cumulative probability of relapse was 0.50.[3]

Measures

Predictors of outcome measured at intake were mainly derived from the SADS, which was administered as soon as possible after admission to treatment (e.g., after detoxification was complete for those who needed it). The training procedures and reliability of the SADS diagnoses have been reported extensively elsewhere.[6-10] SADS ratings and diagnoses were based on patient interviews, discussions with clinical staff and significant others, and clinical records.

Follow-up statuses for MDD and alcoholism were obtained every 6 months with the Longitudinal Interval Follow-Up Evaluation (LIFE).[11] The LIFE provides a format for charting the course and severity of multiple separate conditions, by week, after entry into the study. The training and clinical assessment methods for this portion of the study have been presented in detail previously.[3] In brief, however, we note that the LIFE interviews were administered by systematically trained clinical interviewers. These interviewers were trained on the diagnostic criteria and on the interviewing methods and techniques of the SADS and SADS-L interviews. In the LIFE interviews, interviewers covered the course of all disorders that had been present at intake into the study or any time during the follow-up. They also screened systematically for the onset of new disorders. The course of all disorders during the follow-up interval was determined by asking subjects about the timing of onset and offset in relation to other dates, such as holidays, the beginning of a season or month, etc.

LIFE ratings indicated the status of alcoholism and MDD, by week, during the 5 years of follow-up. Remission from RDC alcoholism was defined as 26 weeks or more with no evidence of any RDC alcohol symptoms (a score of 1 on the 3-point rating scale, with defined anchor points used to indicate the severity of each nonaffective disorder in the LIFE). The start date of remission was Week 1 of the 26 or more weeks required.

The duration of remission was defined in this manner: 1) to be consistent with the DSM-III-R definition of remission; 2) to measure changes in the status of alcoholism with some stability and clinical significance, rather than shorter, unstable remissions without clinical significance; and 3) to keep the methods of this investigation consistent with our previous work[2,3] for comparative purposes.

Relapse was defined as any occurrence

of RDC alcoholism after 26 weeks of remission as defined above. The start date of a relapse was the first week in which any RDC alcohol symptoms occurred after 26 weeks of remission.

We examined the effects of MDD in two ways. In the first, we required a sustained remission as had been defined by the Collaborative Study investigators. Remission from MDD was thus defined as at least 8 weeks without experiencing anything more than one or two mild symptoms of depression (a score of 1 or 2 on the 6-point scale, with defined anchor points used to rate the severity of each affective disorder). This definition of remission from MDD is standard in Collaborative Depression Study research on the course of MDDs. The starting date of the remission was the first week at the level just described that preceded at least 7 additional weeks at a similar or better level of recovery. A remission was considered to have ended (e.g., the patient to have relapsed) when at least 2 consecutive weeks of depression occurred, with mood and symptoms severe enough to meet definite RDC criteria for MDD. In the second way of analyzing the effects of MDD, we investigated the presence or absence of MDD on a week-by-week basis, regardless of the number or duration of any previous changes.

The duration required for remission of MDD was different from the duration required for alcoholism, reflecting differences between the two disorders. The initial reasoning of the Collaborative investigators on remission of depression has yielded much information on the course of affective disorders, with remission defined as above.

Although our main interest was in the relationship of MDD and alcoholism, we also wanted to control for the effects of drug disorders present in this sample. Thus, we included drug abuse/dependence as an additional time-varying predictor used as a control variable. Remission and relapse of a drug use disorder was defined similarly to the definitions used for alcoholism. Because of the lack of effect for drug disorders in general (see below), we did not analyze specific drug use disorders separately.

Methodological research has been conducted on the psychometric characteristics of the LIFE ratings covering a 6-month interval. Of particular relevance to this study is the reliability of the timing of changes in status of the clinical conditions being investigated. Intraclass correlations were used to investigate this question. The ICC reliability of number of weeks from study entry to first week of remission was 0.95 for affective disorders and 0.71 for all other disorders, including alcoholism and drug use disorder.[11] These coefficients indicate excellent reliability in identifying the point in the follow-up when change occurred.

Data Analysis

We first used odds ratios (ORs) to estimate the association between remissions of alcoholism and MDD and (among patients with remissions in both conditions) the association between relapses of alcoholism and relapses of MDD. The ORs were derived in the standard way from fourfold tables. Next, we used survival analysis that focused on the time (in this case, weeks) to an event of interest. We obtained product-limit estimates of the probabilities of remission and relapse of alcoholism. As noted above, survival analyses are useful because they allow the use of partial data on subjects who die or are lost to follow-up before the end of the study. For all such subjects, their status regarding remission or relapse was determined by their ratings up to the time the ratings ended. Most of the patients with incomplete data had either never remitted from alcoholism or had relapsed at the time their ratings ended.

We used Cox proportional-hazard models with both time-invariant (time-independent) and time-varying (time-dependent) predictors[12-14] of remission and relapse in alcoholism. Time-invariant predictors are predictors that do not change as a function of time over the period of follow-up (variables such as sex) as well as conditions present at intake (e.g., duration of alcoholism at intake). The same set of predictors tested in Hasin et al. in 1991[2] were initially used as time-invariant predictors in preliminary analyses that also included the time-varying status of depression. Thus, we included predictors previously found to be significant. In initial models, we also included time-invariant predictors that were not previously significant (e.g., primary/secondary distinction, identified by order of onset of the current episodes, ASPD, bipolar I) because of the ongoing interest in these variables and the need to determine whether their relationship to outcome changed when the time-varying elements were introduced into the model. Clinical predictors from earlier analyses that remained nonsignificant were dropped from our final models because they were not contributing to an understanding of the relationships of main interest.

Time-dependent predictors (or covariates) are variables whose status can change during the follow-up period. With time-varying predictors, one can examine what actually happens to the disorder of interest if another disorder potentially related to it remains the same or changes. Thus, in these analyses, one examines the course of the outcome of interest subsequent to a change in the status of the time-varying predictors (for example, the probability of an alcoholism relapse subsequent to change or stability in MDD at a given point in the follow-up period).

When analyzing remissions and relapses of alcoholism, remission and relapse of MDD were treated as time-varying predictors. In some analyses (see below), we used an additional time-varying predictor indicating the presence or absence of MDD without regard for the specific duration constraints of remission or relapse. Thus, a depression-free week would be indicated as such, without regard to whether it occurred within a period of remission lasting 8 weeks or longer.

Our initial Cox proportional-hazard models included the main variable of interest, the time-varying status of MDD. We also included the following set of time-invariant predictors: sex, baseline age, marital status, bipolar I, bipolar II, schizoaffective disorder, ASPD, severity of alcohol dependence, severity of alcohol-related social problems, duration of the episode of alcoholism current at intake into the study, primary/secondary status of the episode of alcoholism current at intake into the study (indicating order of onset), and Global Assessment Scale (GAS)[15] score at intake into the study, an overall measure of symptom level and functioning. We included one additional time-varying predictor variable, drug use disorder.

RESULTS

We first present summary data on comorbidity remission and relapse status over the 5 years, without regard to the point during follow-up when these events occurred. Although statistical power is lost by ignoring the time-to-event element, the summary results provide an important general picture of the patterns of the two conditions in this group of patients.

Over the 5 years of follow-up, 84 patients (66.1%) experienced remissions in both alcoholism and depression; 21 patients (16.5%) failed to experience remission in either alcoholism or depression; 10 patients (7.9%) experienced remissions in alcoholism without ever experiencing remission in depression; and 12 (9.4%) expe-

FIGURE 1. Cumulative proportion of patients remitting from alcoholism over 5 years
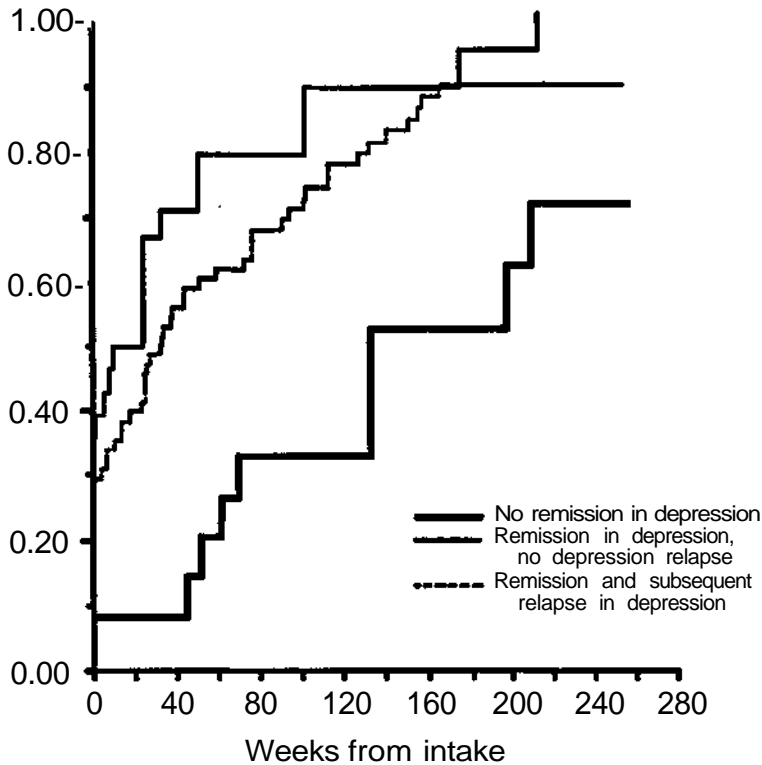
rienced remissions in depression, but no remission in alcoholism.

Remission of the two conditions were highly and significantly associated with each other: the OR indicating the strength of the association was 14.7 (95% confidence interval [CI]: 5.6-38.6). Among patients with remissions in both conditions, 46 (54.8%) had relapses in alcoholism, and 25 (30%) had relapses in MDD. The association of relapse in the two conditions was of borderline significance and of a smaller magnitude than the finding for initial remission: the OR for relapse in alcoholism and depression was 2.7 (95% CI: 0.97-7.47). Of those who had remissions in both conditions, 82 (97.6%) had overlapping remissions in the two conditions; 2 patients were never free of both conditions simulta-

neously during the follow-up; and only 3 patients began remission of alcoholism and depression in the same week.

Cumulative probabilities: remission and relapse of alcoholism. The product-limit cumulative probabilities of experiencing remission in alcoholism, by week in the study, are shown in Figure 1 for the sample subgrouped by depression remission/relapse status. As shown, the cumulative probability of remission in alcoholism was quite high by the end of the 5-year period, although clearly lower for those whose depression never remitted. Among those with a remission in depression, some benefit was retained even among those who subsequently relapsed into another depression, as shown in Figure 1. Figure 2 shows

FIGURE 2.   Cumulative proportion of patients maintaining stable remissions from alcoholism
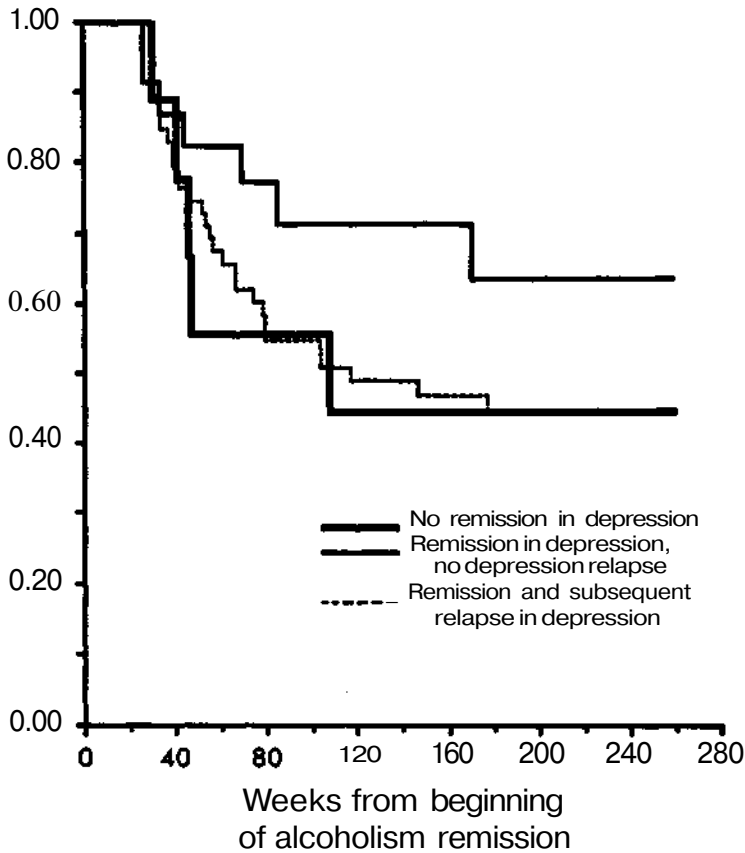

TABLE 1.   Predictors of alcoholism outcome: time from intake to alcoholism remission

Predictor	β	SE(β)	P
	− 0.009	0.010	0.336
Sex	0	0.214	0.639
Bipolar II	1.037	0.377	0.006
Alcohol dependence severity	−0.703	0.235	0.003
Drug disorder remission	0.762	0.280	0.190
Depression, first remission	0.977	0.379	0.006
Depression, second remission	0.778	0.593	0.010

TABLE 2.   Predictors of alcoholism outcome: time from alcoholism remission to subsequent relapse

Predictor	β	SE (β)	P
Age	−0.028	0.016	0.078
Sex	−0.593	0.340	0.081
Bipolar II	−0.581	0.608	0.339
Alcohol dependence severity	− 0.153	0.340	0.652
Drug disorder remission	− 0.365	0.494	0.460
Depression remission	− 0.192	0.390	0.002

the product-limit cumulative probability of maintaining stable remissions in alcoholism without relapse. Figure 2 uses as a starting point the week in which the remission began. As shown, the probability of relapse into alcoholism was quite high by the end of the 5-year period. When the sample was divided into sub-groups consisting of those with no remission in depression, those with remission of depression but then subsequent relapse, and those with stable remissions in depression, the group with the stable remissions in depression had the lowest cumulative probability of relapse in alcoholism.

Cox models: remission in alcoholism. The first Cox model included all demographic and clinical control variables listed above; a time-varying drug disorder control variable; and variables representing first, second, third, and fourth depression remissions. In this full model, the first and second remissions of MDD significantly predicted alcoholism remission, although subsequent changes in depression status did not. The drug disorder variable was not significantly related to alcoholism remission, nor was ASPD, primary/secondary status, bipolar I, schizoaffective disorder, or demographic variables. The only two time-invariant predictor variables that remained significantly associated with alcoholism remission were bipolar II disorder and severity of alcohol dependence. These findings remained essentially unchanged in a reduced model (Table 1).

To eliminate concerns that the duration required in our definition of depression remission had somehow biased the results of the analysis, we re-ran the reduced model with a variable representing remission of MDD as only a depression-free week. Thus, the constraints of the depression duration requirement were removed. In this second model, depression remained a significant predictor of alcoholism remission *(P = 0.016)*. No other variables changed from significant to nonsignificant in this second model, or vice versa.

Cox models: relapse in alcoholism. Next, we examined predictors of relapse in alcoholism. Remission from depression significantly reduced the chances of an alcoholism relapse. None of the other control variables were significant when they were all included in the model. We show a reduced model (Table 2) with the same variables that were included in Table 1. Thus, drug use disorder, bipolar I, ASPD, primary/secondary (order of onset of the current conditions), and the demographic variables were not significantly related to alcoholism relapse. (In some of the analyses that did not include the drug disorder variable, sex and age shifted back and forth between significance and nonsignificance. Because of the instability of these results and the fact that age and sex were not significant when we controlled for drug disorder, we do not attribute much importance to their marginal level of relationship to the outcome of alcoholism relapse.) To investigate again whether a depression predictor variable maintained a significant relationship to alcoholism when the time constraints of remission were removed, we re-ran the analysis with the depression variable recoded to represent any depression-free week. In this model, the significance of the relationship of depression status to alcoholism relapse was strengthened *(P < 0.0001)*.

DISCUSSION

To our knowledge, this report represents the first attempt to use clinical status ratings throughout an extended period of follow-up to examine the effects of MDD on alcoholism. The results clearly indicate that in this sample of patients with serious affective disorders and comorbid alcoholism, the status of the affective disorder had a

relationship to the alcohol use disorder. We had previously been unable to predict relapses in alcoholism in this sample. However, the time-varying predictors reflecting depression status during the follow-up provided a considerably more informative picture. Remission in MDD significantly improved the outlook for a remission in RDC alcoholism in these patients, and significantly reduced the chances of an alcoholism relapse. These effects were strong enough to emerge even though the sample and some subgroups were only moderate in size. Also, the results were stable in multiple models that included many control variables often assumed to exert a strong influence on alcoholism.

The severity level of alcohol dependence remained significant in predicting remission in RDC alcoholism even with MDD in the model. The fact that this variable was still significant and also that it did not have any effect on the prediction of MDD[16] shows that 1) dependence severity was a specific and robust predictor of alcoholism remission in these patients, and 2) separation of abuse-related problems (i.e., alcohol-related social problems) and dependence indicators remains a valid concept in the measurement of alcohol-related conditions.

We had previously shown that bipolar II status and a schizoaffective diagnosis before study intake were related to the outcome of alcoholism. The damaging effect of the schizoaffective disorder was no longer significant when we included clinical status of MDD in the analysis. The schizoaffective diagnosis may have exerted its earlier effect through chronicity/severity of the affective condition, an effect now absorbed by the inclusion of major depressive syndrome in the follow-up status in the present analyses. The apparent protective effect of bipolar II remained significant even with status of MDD included in the model. We had examined this finding closely in the earlier paper but were not

able to find an explanation for it, which is still the case. Given the lack of explanation, we can only hope that data will become available to replicate the effect. If replicated in another sample, then the implications of this finding will need to be investigated thoroughly.

A consistent finding across all three reports was that the diagnosis of ASPD was unrelated to the outcome of alcoholism. Although some investigators have found this finding surprising, we note that Woody et al.[17] found that addicted persons with ASPD who were also depressed responded to treatment, whereas addicted persons with ASPD who were not depressed were unresponsive to treatment. These differences reflect the heterogeneity of diagnostic categories. Because all of our subjects had both alcoholism and depression, the lack of an adverse effect of ASPD is consistent with the work of Woody et al.[17]

In this article, as in previous reports, we examined the course of alcoholism, but not of drinking per se. As we discussed previously, alcohol consumption and alcoholism are related but distinct phenomena. Alcohol consumption was not measured systematically enough in the Collaborative Depression Study to perform the above analyses with drinking status or drinking level as a time-dependent covariate. The collection and analysis of such information should be included in future studies of this type.

Although some patients received treatment for affective, alcohol, or other conditions, treatment was not randomly assigned and treatment status was not included in the above analyses. The patients in the sample had a wide variety of treatment experiences for their alcohol problems, ranging from none to multiple hospitalizations. We showed previously that treatment for alcohol disorder was not significantly related to the outcome of alcoholism,[2] perhaps because some patients with milder alcohol problems had no treat-

ment, whereas some patients with the worst problems had the most treatment but did not recover. Given our previous results, the nonrandom nature of the treatments received, and the potential complexities of the relationships between severity, selection into treatment, and treatment effects and outcome, we did not include treatment as a covariate because of the high potential for biased and possibly misleading results.

As noted, the primary/secondary distinction of the current episode (order of onset) did not prove to have a significant relationship with outcome, either in earlier reports or in the present analyses. We did not include the primary/secondary distinction of the initial episode for two reasons: 1) the reliability of this distinction is poor,[9] and 2) this investigation focused on the course of two conditions in existence at a certain point in time, and not on their initial etiology. Although a comprehensive review of the primary/secondary issue is beyond the scope of this article, note that in family studies, the initial occurrence of alcoholism or depression appears to make a difference in familial distribution of disorders (as reviewed by Coryell and colleagues[18]), but that the initial primary/secondary difference does not appear to have an effect on the ongoing course of the disorders once they have both begun.[19-21]

Other work from the Collaborative Depression Study has addressed the relationship between alcoholism and depression, but all papers, aside from the three cited above,[1-3] have reported on investigations of depression or other affective disorders as the conditions of main interest, using alcoholism as a predictor variable. Given that this investigation addressed alcoholism as the main outcome of interest and used many alcohol-specific variables as predictors, it differs considerably from other work of the Collaborative Depression Study.[22,23]

In this group of patients, drug use/ abuse was not a frequently reported problem. However, to ensure that our findings were not spuriously affected by drug problems in this sample, we included the status of drug use disorders as a time-varying control variable in the multivariate analyses. The results showed that drug disorders did not affect the main relationships investigated. However, the relationship of drug use disorders to alcoholism in the presence of MDD should be investigated with similar methodology in other samples of subjects, for example, those with serious drug problems.

Previous studies have demonstrated that among patients hospitalized in alcohol-identified treatment facilities, depressive symptoms present at admission often remit by the end of several weeks of hospitalization unless there are particular social problems.[24-27] The few studies that addressed the relationship of depression to alcoholism among such patients over extended, nonhospitalized periods of time[28-31] measured depressive symptoms, rather than clinician-assessed depressive disorders. To our knowledge, no previous studies have used psychiatric patients as a sample, have clearly addressed the order of changes in depression and alcoholism within a follow-up period, or have assessed the impact of recurrence of depression at times when patients are vulnerable to alcoholism relapse, for instance, after discharge from treatment. If additional studies of patients in substance-focused treatment settings or in general population settings using similar methodology showed consistent findings with the results presented above, then the combined findings would suggest value in developing clinical trials of treatments for alcoholism designed specifically to take both MDD and alcoholism into account.

The resources and effort required to carry out the type of longitudinal research that produces data such as those presented above are considerable. However, there is

really no way to replace data of this type when attempting to answer questions about potentially closely linked phenomena that occur over the extended course of chronic, if intermittent, disorders. The use of time-varying predictors allowed us to make use of this information, in a manner that (to our knowledge) has not been used previously in the study of psychiatric comorbidity. We have focused our analyses on patients with alcoholism and serious affective disorders. However, the questions concerning the relationships of alcohol (and drugs) to many other psychiatric conditions remain unanswered. Parallel studies on these relationships should be conducted with additional types of clinical samples and with more demographically diverse patients, including black and Hispanic patients, as well as in the general population. Such studies would provide empirical data to clarify clinical impressions about the nature of the relationships between alcohol, drugs, psychiatric symptoms, and disorders.

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