

Research report

Five-year course of major depression: Effects of comorbid alcoholism

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Abstract

Some patients enter psychiatric treatment with clear cases of both major depression and alcoholism. While assumptions are often made about the relationships of these two conditions, little empirical evidence exists on the effects of sustained remissions in alcoholism on sustained remissions in depression. 127 patients with both disorders at treatment entry were studied over a 5-year period. Survival analyses with time-dependent covariates indicating alcoholism status were used to investigate remissions and relapses in major depression. Remission in alcoholism strongly and significantly increased the chances of remission in depression and were also related to reduced chances of depression relapse, although at a weaker level.

Keywords: Depression; Alcoholism; Comorbidity; Longitudinal course

1. Introduction

Until the mid-1980s, little empirical information existed about the influence of alcoholism on the longitudinally assessed course of major affective disorders. As data became available from the NIMH Collaborative Depression Study of psychiatric patients with serious affective disorders (Katz and Klerman, 1979), investigators began to study the effects of alcoholism on depression in various ways.

In an early report on the 'dual-diagnosis' issue, Hasin et al. (1985) showed that nearly a quarter of the Collaborative Depression Study patients had clinically significant alcohol problems just prior to treatment (usually hospitalization for their affective disorder). Hirschfeld and colleagues showed that in a subset of the Collaborative Study sample limited to patients with unipolar depression, the presence or absence of alcoholism at study intake did not predict sharp differences in the outcome of major depression (Hirschfeld et al., 1990). Mueller et al. (1994) also studied the course of unipolar depression. They focussed on week-to-week transitions into and out of

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major depression, regardless of how long the transitions persisted. These weekly transitions were compared between patients with current alcoholism, past-only alcoholism, and those who were never alcoholic. In this investigation, transitions *out* of major depression (analogous to remissions, although without a duration requirement) were more likely to occur among patients with past-only alcoholism or those who had never been alcoholic. Transitions *into* major depression (analogous to relapse without a duration requirement) did not differ by alcoholism status.

The reports of Hirschfeld, Mueller and colleagues offer important information on differences in the course of unipolar affective disorder between those with and without alcoholism. However, they do not address a number of clinically important questions in an area that is still relatively unresearched. For example, there is still no published information on the effects of changes in the clinical status of alcoholism on the outcome of depression among a group of patients who *all* start out with both alcoholism and an affective disorder. Previous reports do not address the question of whether any effect of alcoholism is altered by whether the patient has a unipolar, bipolar or schizoaffective disorder. Also, the earlier studies do not provide information on the effects of changes in alcoholism status on sustained changes in the status of the affective disorder, a question often of considerable interest to both patients and clinicians. In this paper, we continue the investigation of the effects of alcoholism on affective disorders. Among a group of patients with clearly diagnosed cases of both alcoholism and a serious affective disorder, we analyze the effect of remissions in alcoholism on sustained remissions and subsequent relapses in major depression over a 5-year period. We included unipolar, bipolar and schizoaffective patients, and controlled a number of potentially confounding variables.

2. Methods

2.1. Subjects

Subjects were psychiatric patients in the clinical studies portion of the NIMH Collaborative Depres-

sion Study. The general methods of the study have been described elsewhere (Katz and Klerman, 1979). 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) (Spitzer et al., 1978), based on evaluation with the Schedule for Affective Disorders and Schizophrenia (SADS) (Endicott and Spitzer, 1978) and a review of medical records. 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 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 a quarter of the patients were from Iowa, another quarter from Boston, a third from St. Louis and the rest were from New York and Chicago. At intake into the study, 88% were psychiatrically hospitalized, while the remainder were outpatients. The affective disorders were severe, and were required to be non-organic by the RDC criteria. While the minimum duration of affective disorders for RDC was 2 weeks, most patients had been depressed considerably longer. The types of affective diagnoses received by these patients were: 5% schizoaffective disorder, 13% bipolar I, 8% bipolar II and 74% unipolar major depressive disorder (Hasin et al., 1989). All gave informed consent to participate.

As noted earlier (Hasin et al., 1991), the overall 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. This indicated that some of the patients had milder problems with alcoholism than would be seen in an inpatient alcohol-identified treatment facility.

Of the 127 patients, 97 were followed 5 full years. Ten patients died before the end of the follow-up (five of suicide, two of cancer, and three of other

alcohol-related causes; Hasin et al., 1989), 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 specifically designed to use all available data on subjects, even those who died or dropped out prior to the end of the study period (see below).

Note that the follow-up portion of the CDS was entirely a naturalistic study with regard to treatment. This was true for all disorders, including the affective disorders as well as the alcoholism experienced by these patients. In prior analyses (Hasin et al., 1989), we found that treatment for alcoholism was not related to the outcome of the alcohol use disorders in this sample.

2.2. Measures

The predictors of outcome that were 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 (Spitzer et al., 1978; Endicott and Spitzer, 1978; Gibbon et al., 1981; Andreasen et al., 1981, 1982). SADS ratings and diagnoses were based on patient interviews, discussions with clinical staff and significant others, and clinical records.

Follow-up status for major depression and alcoholism was obtained every 6 months with the Longitudinal Interval Follow-up Evaluation (LIFE) (Keller et al., 1987). 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 previously (Hasin et al., 1989).

LIFE ratings indicated the status of alcoholism and major depression, by week, during the 5 years of follow-up. Recovery from a major depressive syndrome was 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 six-point scale with defined anchor points used to rate the severity of each affective disorder, Mueller

et al., 1994). This definition of recovery from major depression has been used in many of the CDS reports. Relapse was defined as 2 weeks (or longer) of any re-occurrence of major depression following 8 weeks of recovery as defined above.

While most control variables in the analysis were derived from information gathered at intake, we did include one time-varying control variable that was derived from LIFE data, drug use disorder. Due to the lack of effect for drug disorders in general (see below), we did not analyze drug use disorders separately.

Methodological research has been conducted on the psychometric characteristics of the LIFE ratings. Of particular relevance to this study is the reliability of the timing of changes in status of the clinical conditions being investigated. The intraclass correlation was 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 (Keller et al., 1987). These coefficients indicate excellent reliability in identifying the point in the follow-up when change occurred.

2.3. Analysis

We first used odds ratios to estimate the association between remissions of alcoholism and recovery from major depression and (among patients with remissions in both conditions) the association between relapses of alcoholism and relapses of depression. The odds ratios were derived in the standard way from 4-fold tables. These odds ratios did not take any account of the sequencing of recovery in the two conditions. Next, we used survival analyses that focussed 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 depression.

We then used Cox proportional hazard models with both time-varying (time-dependent) and time-invariant (time-independent) predictors (Cox, 1972; Cox and Oates, 1984; Kalbfleish and Prentice, 1980) to investigate recovery from major depression and subsequent relapse. In these analyses, changes in the status of depression (remission and relapse) were the outcome variables. Time-invariant predictors are familiar to most researchers. These include variables

assessed at admission to the study that do not change as a function of time over the follow-up. Examples of time-invariant predictors are sex or the duration of alcoholism at intake. A limitation in relying only on such fixed predictors is that patients' conditions can change in important respects during the follow-up in ways that may be related to the subsequent course of their depression. The use of time-varying predictors overcomes this problem by allowing the flexibility of investigating the effects of changes in predictor conditions on the subsequent course of the depression. These survival analyses specifically take account of the *sequencing* of changes. In this report, the main time-varying predictor was the status of alcoholism. Also included as a control variable was the status of drug use disorder.

Our initial Cox proportional hazard models included the main predictor variable of interest, the time-varying status of alcoholism. We also included the following set of time-invariant predictors: sex, baseline age, marital status, bipolar I, bipolar II, schizoaffective disorder, antisocial personality disorder (ASP), 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, and Global Assessment Scale (GAS) score (Endicott et al., 1976) at intake into the study, an overall measure of symptom level and functioning. These variables had been used in conjunction with major depression in earlier analyses of the outcome of alcoholism in these patients (Hasin et al., 1989, 1991), although only two (bipolar II and alcohol dependence severity) had been significant in final models predicting the outcome of alcoholism when depression was included in the model as a time-varying predictor (Hasin et al., 1996). In the present analyses, we also included one additional time-varying predictor variable, drug use disorder. We showed previously (Hasin et al., 1996) that the time-dependent drug predictor variable was not significantly related to the outcome of alcoholism in this sample.

3. Results

Summary information is presented first, to give a general overview of the outcome of these patients.

While this information ignores the important time-to-event element, it provides a framework for the more detailed information to follow.

Over the 5 years of follow-up, only 21 patients (16.5%) failed to experience any remissions in either alcoholism or depression. Eighty-four patients (66.1%) experienced at least one remission in both alcoholism and depression. Ten patients (7.9%) experienced at least one remission in alcoholism without ever experiencing remission in depression, and 12 (9.4%) experienced at least one remission in depression but no remission in alcoholism.

Remissions of the two conditions were highly and significantly associated with each other: the odds ratio indicating the strength of the association was 14.7 (95% confidence interval 5.6, 38.6). Among patients with remissions in both conditions, 46 (54.8%) had relapses in alcoholism, and 25 (30%) had relapses in major depression. The association of relapse in the two conditions was of borderline significance and of a smaller magnitude than the finding for initial remission: the odds ratio of relapse in alcoholism and depression was 2.7 (95% confidence interval 0.97, 7.47). Of those who had remissions in both conditions, 82 (97.6%) had overlapping remissions in the two conditions; two patients were never free of both conditions simultaneously during the follow-up. Only three patients began remission of alcoholism and depression in the same week (Hasin et al., 1996).

3.1. Cumulative probabilities: remission and relapse of depression

The overall probability of remission in depression was high (Fig. 1). The chances of a depression remission for at least 2 months were greatly improved among those who also experienced a remission in alcoholism. This did not appear to be affected by subsequent relapse of the alcoholism. However, the chances of depression remission were clearly worse among those whose alcoholism did not remit at all.

Fig. 2 shows the cumulative probability of relapse in depression among those who experienced remissions in this condition. As shown, the probability of depression relapse was quite high. When the sample

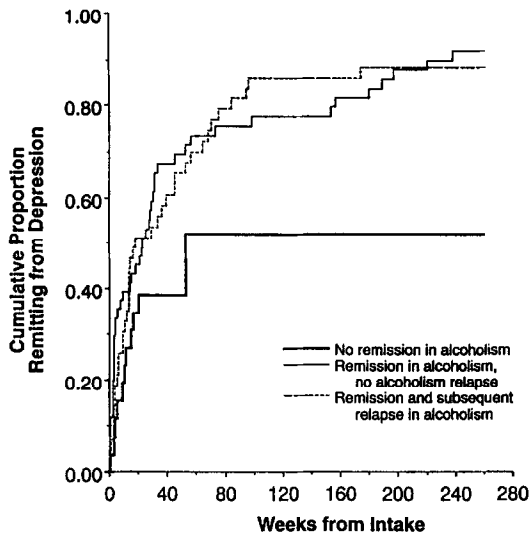


Fig. 1. Cumulative proportion of patients remitting from depression over 5 years, by alcoholism status.

was subgrouped into those who had no remission of alcoholism, those who had a remission of alcoholism followed by subsequent relapse, and those who had a remission of alcoholism that remained stable, the figure shows that those without remissions in alcoholism had the highest probability of relapse in their depressions.

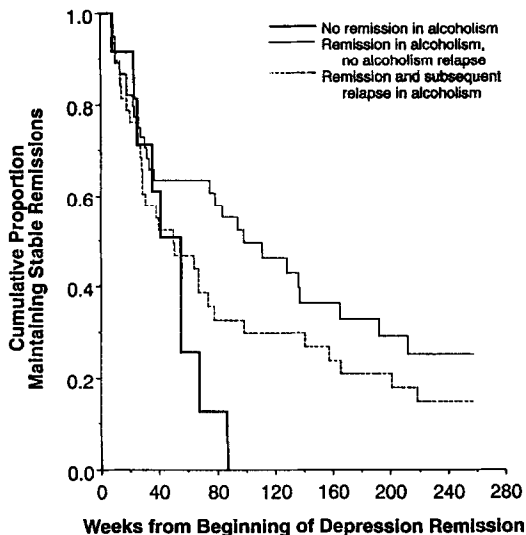


Fig. 2. Cumulative proportion of patients maintaining stable remissions from depression (e.g., no relapse) over 5 years, by alcoholism status.

3.2. Cox models: Remission in depression

The first full model run included all the control variables listed above. This model indicated that none of the clinical variables, including those that had significantly predicted alcoholism outcome in this sample (Hasin et al., 1991) were significantly related to time-to-remission of major depression. Thus, subtype of affective disorder, severity of alcohol dependence, and primary/secondary status of the current episode of alcoholism were not predictive of depression outcome in this sample of patients with both conditions. Similarly, neither the drug disorder variable or the demographic variables were significantly associated with depression outcome. However, alcoholism remission was quite a robust predictor of subsequent depression remission.

Given this initial result, subsequent reduced models were run. Table 1 indicates the results of a model that includes a smaller number of variables. As shown, alcoholism status was related to depression outcome at a highly significant level. In an additional model that included only age, sex, and a reformulated alcohol variable indicating any week free of alcoholism, alcoholism remained a highly significant predictor of sustained remission (2 or more months) in depression ($\beta = 0.5332$, $SE(\beta) = 0.2163$, $P = 0.014$).

3.3. Cox models: Relapse in depression

The full model once again demonstrated that the clinical variables aside from alcoholism were not significantly related to depression relapse. While most of the demographic variables were also not related, sex showed an effect, with females more

Table 1

Predictors of depression outcome: time from intake to depression remission

Predictor	β	$SE(\beta)$	P
Age	0.0000	0.0090	0.957
Sex	-0.0874	0.2218	0.694
Bipolar 2	0.2420	0.3692	0.512
Alcohol Dependence Severity	0.0259	0.2275	0.909
Drug Disorder Change	0.6906	0.5432	0.204
Alcohol Remission	0.5500	0.2363	0.020

Table 2

Predictors of depression outcome: time from depression remission to subsequent relapse

Predictor	β	SE(β)	P
Age	0.0062	0.0119	0.601
Sex	0.6093	0.2586	0.019
Bipolar 2	0.4497	0.4894	0.358
Alcohol dependence severity	0.1514	0.2687	0.573
Drug disorder change	-0.3361	0.6727	0.617
Alcohol remission	-0.7300	0.3119	0.019

likely to relapse. The reduced model (Table 2) shows that alcoholism remained significantly related to depression relapse, although not as strongly as for depression remission. In a model that included only age, sex and the reformulated alcoholism variable (any week free of alcoholism without a duration requirement), alcoholism was the only significant predictor of depression relapse, although again, the effect was somewhat weaker ($\beta = -0.525$, SE(β) = 2644, $P = 0.047$).

4. Discussion

Among this sample of patients who entered treatment with severe affective disorders and alcoholism, the course of the alcoholism had an effect on the course of depression. Examining sustained remissions in depression and the effects of sustained remissions of alcoholism showed that improvement in alcoholism was highly associated with better outcome for depression. At a somewhat weaker level, remissions in alcoholism also appeared to have a protective effect against depression relapse.

As described above, we found that clinical predictors of the outcome of alcoholism in this sample were not related to the outcome of depression. The fact that the predictors were related differently to the two outcomes attests to the validity of the two separate sets of results.

In this paper, as in previous reports, we examined the course of alcoholism but not of drinking per se. As discussed previously, alcohol consumption and alcoholism are related but distinct phenomena. Alcohol consumption was not measured systematically

enough in the CDS study to perform the above analyses with drinking status or drinking level as a time-dependent covariate. In future studies, the addition of such a variable would provide additional useful information.

Drug disorders did not prove to be significantly related to outcome in this sample. However, it may be that other psychiatric samples would show different results for drug use disorders (preparations for such a study are now underway, and will be reported later when data is available). Additionally, while some patients in the present study received treatment for affective, alcohol or other conditions, these were not randomly assigned and treatment status was not included in the above analyses. We found previously that treatment for alcohol was not significantly related to outcome of the alcohol condition (Hasin et al., 1989). Given our previous results, the non-random nature of the treatments received, and the potential complexities of the relationships between severity, selection into treatment, any treatment effects and outcome, we did not include treatment as a covariate due to the potential for biased results.

As noted, the primary/secondary distinction of the current episode of alcoholism did not prove to have a significant relationship with outcome of depression or alcoholism, either in earlier reports or in the present analyses. We did not include the primary/secondary distinction of the initial episode of alcoholism for two reasons. First, the reliability of this distinction is poor (Andreassen et al., 1981). Second, the focus of this paper was on the course of conditions that were both in existence at a certain point in time and not on their initial occurrence, which may have occurred under considerably different circumstances many years earlier. While a comprehensive review of the primary/secondary issue is beyond the scope of this paper, note that in family studies, the initial order of occurrence of alcoholism or depression appears to make a difference in familial distribution of disorders (as reviewed by Coryell et al., 1992), but that the initial primary/secondary different does not appear to have an effect on the ongoing course of the disorders once they have both begun (O'Sullivan et al., 1988; Powell et al., 1992; Zisook and Schuckit, 1987).

Among patients hospitalized in alcohol-identified treatment facilities, depressive symptoms present at

admission often show considerable improvement after several weeks of hospitalization unless particular social problems exist (Gibson and Becker, 1973; Brown and Schuckit, 1988; Nakamura et al., 1983; Overall et al., 1985). The few studies that investigated the relationship of depression and alcoholism among such patients over extended, non-hospitalized periods of time (Behar et al., 1984; Hatsukami and Pickens, 1982; Pettinati et al., 1982; Pottenger et al., 1978) measured depressive symptoms rather than clinician-assessed depressive disorders. To our knowledge, no previous study has used psychiatric patients as a sample or clearly addressed the order of changes in depressive disorders and alcoholism during a non-hospitalized follow-up period. If additional studies of patients in different types of settings or in general population samples show findings consistent with the results presented above, then the combined findings would suggest value in developing clinical trials of treatments (including psychosocial treatment) that specifically take aspects of both disorders into account. In addition, such studies should include a wider range of patients in terms of demographic characteristics, including non-white patients and patients from outpatient treatment settings.

The fact that alcoholism remission was significantly related to remission and relapse of major depression suggests the possibility that clinicians who ignore concurrent alcoholism in depressed patients run the risk of providing inadequate treatment for both conditions, not just the alcoholism. Some clinical trials are now being conducted to investigate this possibility. However, while awaiting their results, it appears that numerous clinicians in psychiatric and other mental health facilities remain uncomfortable addressing issues related to alcoholism, may wish that patients with both conditions would seek treatment elsewhere, and may not know standard techniques for assessing and treating substance abuse (whether alcohol or drug), such as recognizing and dealing with denial. Although understanding of this problem has been improving in recent years, perhaps this paper and others will help stimulate educational efforts as well as continuing efforts to develop more effective treatments for patients with 'dual-diagnosis' problems.

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