ORIGINAL ARTICLE

The Effect of Depression on Return to Drinking

A Prospective Study

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Background: The effect of depression on return to drinking among individuals with alcohol dependence is controversial. From February 1, 1993, to April 15, 1996, we consecutively recruited 40 women and 61 men hospitalized for alcohol dependence and followed them up monthly for 1 year to assess the effect of depression on drinking outcomes.

Methods: We conducted structured interviews during hospitalization and monthly following discharge for 1 year to determine whether depression at treatment entry affected the likelihood of return to drinking and whether this effect differed between sexes. Using survival analysis, we examined the effect of depressive symptoms and a diagnosis of current major depression at treatment entry on times to first drink and relapse during follow-up.

Results: A diagnosis of current major depression at the time of hospitalization was associated with shorter times to first drink (hazard ratio, 2.03; 95% confidence interval [CI], 1.28-3.21; P=.003) and relapse (hazard ratio, 2.12; 95% CI, 1.32-3.39; P=.002). There was no significant difference between women and men in this effect. Depressive symptoms as measured by the Beck Depression Inventory did not predict time to first drink or relapse in women or men.

Conclusions: A diagnosis of current major depression at entry into inpatient treatment for alcohol dependence predicted shorter times to first drink and relapse in women and men. Our results differ from earlier reports that men and women differ in the effect of depression on return to drinking.

Arch Gen Psychiatry. 1998;55:259-265

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ALTHOUGH DEPRESSION and alcohol dependence commonly coexist in community and treatment-seeking populations,[1-5] there is no clear consensus on appropriate assessment and treatment of patients who present with symptoms of both disorders.[2,6-9] To make appropriate treatment decisions, clinicians must know the likely effects of depression on drinking outcomes.[10] Although previous studies have demonstrated the course of depressive symptoms during abstinence from alcohol,[7,11] information regarding the effect of depression on the likelihood of return to drinking is sparse and contradictory.[4,12-22]

Several studies have reported better drinking outcomes for women with depression,[4,21] whereas 1 study found worse drinking outcomes for depressed men.[4] A study of 227 patients (77% male) seeking treatment for alcohol dependence[4] found that women with a lifetime diagnosis of major depression had better drinking outcomes 1 year following hospitalization than did women with other co-occurring psychiatric diagnoses or alcohol dependence alone, whereas men with major depression had poorer drinking outcomes. However, at 3-year follow-up, this gender difference disappeared, and a lifetime diagnosis of major depression was associated with reduced drinking intensity for men and women.[22] In contrast, a 5-year follow-up of subjects with concurrent major depressive disorder and alcohol dependence found that remission of major depressive disorder predicted remission of alcohol dependence,[14] regardless of sex or the distinction of primary vs secondary depression.

These contradictory conclusions may have resulted from study samples that were small,[17] were single-sex,[15-17,21] had few women,[12] had gender differences in prevalence rates of primary or secondary psychiatric disorders,[4,11,22] or varied in other key sociodemographic characteristics.[23] In addition, the use of long time windows (ie, time between assessments) in some stud-

SUBJECTS AND METHODS

SUBJECTS

We recruited 101 consecutive alcohol-dependent subjects from the inpatient unit of the Alcohol and Drug Abuse Treatment Program, McLean Hospital, Belmont, Mass. Patients were eligible for the study if they were 18 years of age or older and met criteria for a diagnosis of alcohol dependence as determined by the Structured Clinical Interview for *DSM-III-R* (SCID-III-R).[27] Subjects with and without other Axis I diagnoses, including other substance use disorders, were eligible. For subjects who used other drugs, we ascertained that alcohol was the primary substance of abuse by asking the following 3 questions: Which of these drugs (1) has caused you the most difficulties? (2) do you use most frequently? and (3) is your primary drug of use? The subject had to answer alcohol to all 3 questions to be included. Exclusion criteria included living too far away to return for follow-up and cognitive impairment that interfered with the subject's ability to adhere to the study protocol.

STUDY PROCEDURES

Subjects underwent screening and recruitment in the hospital after detoxification. After signing informed consent, subjects underwent evaluation using structured interviews and self-report questionnaires in two 2-hour sessions. Axis I diagnoses were made using the SCID-III-R.[27] Because of the difficulty involved in distinguishing addiction-related symptoms from enduring personality traits,[28,29] we assessed only antisocial personality disorder among the Axis II disorders. This diagnosis has been subjected to the most extensive reliability and validity testing of all the personality disorders[30] and includes criteria regarding age at onset, which helps distinguish symptoms of antisocial personality disorder from behavior related to drug dependence.

As in previous studies,[31] to examine validity of subject self-reports during follow-up , subjects were asked to designate a collateral informant to be called during follow-up. At hospital discharge, prescription of antidepressants by the hospital psychiatrist was recorded. Following discharge, subjects were interviewed in person monthly for 12 months to assess drinking outcomes, mood symptoms, and treatment activities. Subjects were paid $10 per visit.

MEASUREMENT OF ALCOHOL USE

Sociodemographic information and lifetime history of alcohol and other drug use were obtained using the Drug and Alcohol Use Questionnaire, a 138-item self-report instrument used for this purpose in previous studies.[32,33] The Addiction Severity Index (ASI), a well-validated assessment of severity of substance-related problems,[34] was used to assess the severity of substance use and family, social, psychological, medical, and legal problems in the 30 days before hospitalization and each 30-day follow-up interval. The Timeline Follow-back assessment method,[35] a standardized interview that uses a calendar and documents actual calendar days, was used to assess the number of drinking days and the number of drinks per drinking day in the 30 days before hospitalization and each 30-day follow-up interval.

At each monthly visit, we performed a supervised urine toxicologic screen and breath alcohol test. Positive results from an intoxication breath testing device (Breathalyzer) or self-report was considered evidence of drinking. Because subject reliability decreases during intoxication,[36,37] subjects with positive results of the breath alcohol test were asked to return for the follow-up interview within several days. Within 1 week of each subject's monthly visit, a collateral informant was interviewed by telephone regarding the subject's drinking outcomes.

MEASUREMENT OF DEPRESSION

Depressive symptoms were measured with the 22-item Beck Depression Inventory (BDI),[38] which has been shown in several studies[39-41] to be a reasonably reliable measure of

ies[4,18,22] may have affected outcomes by subjecting the assessment of drinking behavior[10] or depressed mood in the interval to poor recall or recall bias.[24] Study outcomes may also vary according to whether depression is measured by diagnosis or symptom rating scales[4,14,22] or whether depression is primary or secondary.[16,25] Finally, potential differences in using lifetime vs current diagnosis of depression when measuring short-term drinking outcomes have been relatively unexplored.[26]

In our study of 60 men and 41 women hospitalized for alcohol dependence, we examined the relationship between depression at treatment entry and drinking outcomes. Depression was measured categorically by diagnosis and continuously by symptom ratings. Monthly follow-up visits for 1 year following hospital discharge were used to minimize poor recall and recall bias and to increase validity of self-reports in our assessment of drinking outcomes. The study was designed to answer the following questions: (1) What is the effect of depression during hospitalization on drinking outcome during the year following discharge? (2) Does this effect differ according to whether depression is measured by diagnosis or symptoms? (3) Does the relationship between depression and drinking outcome differ by sex?

RESULTS

SOCIODEMOGRAPHIC CHARACTERISTICS

The sociodemographic characteristics of the sample are summarized in **Table 1**.

BASELINE DRINKING CHARACTERISTICS OF SUBJECTS

Baseline drinking characteristics are summarized for the total sample and by major depression diagnosis in **Table 2**. There were no significant differences in any ASI subscale scores in the 30 days before hospital admission between those with and without a diagnosis of current major depression.

depressive symptoms in patients with substance use disorders.

Diagnosis of current major depression was made using the SCID-III-R.[27] Because our goal was to examine the proximal effect of major depression on drinking outcomes, we chose to examine the effect of current rather than lifetime diagnosis of major depression on drinking outcomes following hospitalization. A diagnosis of current major depression was made if the subject met at least 5 of 9 criteria every day for 2 weeks at any time during the 6 months before admission. We chose the previous 6 months as the time for current depression because research has shown that reliability of a depression diagnosis is in the moderate to acceptable range within 6 months, and reliability of diagnosis may become unstable after this time.[42]

All subjects entering the hospital for treatment of alcohol dependence had been actively drinking before admission. Previous work[43] has demonstrated the difficulty of distinguishing enduring mood and other psychiatric symptoms from those that are substance induced. Research groups have addressed this issue in various ways.[42-47] We decided to include all subjects who met criteria for current major depression in the 6 months before admission, regardless of their drinking status when these symptoms occurred. We then distinguished primary from secondary depression using an interview form based on previous research criteria.[48] Thus, if the onset of major depression occurred before the onset of alcohol dependence, or if major depression was present during abstinence of at least 3 months' duration, then the depression diagnosis was coded as primary. Otherwise, major depression was coded as secondary.

OUTCOME DEFINITIONS

We used times to first drink and relapse as the 2 primary measures of drinking outcomes. A conservative definition of relapse was chosen based on previous work[49] demonstrating that risks of alcohol consumption increase at approximately 60 g/d for men and 40 g/d for women. A standard drink is defined as 13.6 g of absolute alcohol.[35] Relapse was, therefore, defined as 3 or more standard drinks on a drinking day for women and 5 or more standard drinks on a drinking day for men.[49]

STATISTICAL ANALYSIS

All dichotomous variables were analyzed using the χ^2 test. The Fisher exact test was used to analyze dichotomous variables when expected cell frequencies were less than 5. In the case of a nominal independent variable (eg, sex) and an ordinal independent variable with multiple levels (eg, education), we used the Cochran-Mantel-Haenszel trend test.[50] Continuous variables were analyzed using the Student *t* test for a comparison of means. All of these analyses were conducted using the statistical software program SPSS for Windows 95.[51] Statistical significance was defined as $P \leq .05$, and *P* values were all 2-tailed. Using statistical methods for survival data, we analyzed the effects of sex and depression on times to first drink and relapse. Survival calculations were performed using EGRET software.[52] The primary independent variables were sex, *DSM-III-R* diagnosis of current major depression,[53] and initial BDI score. In the first survival analysis, the Cox proportional hazards model[54] used sex, BDI score, and sex times BDI score to predict times to first drink and relapse. In the second survival analysis, the Cox proportional hazards model used sex, current major depression diagnosis, and current major depression diagnosis times sex to predict times to first drink and relapse. For each survival analysis, we adjusted the model for the following covariates: age, marital status, education, employment, primary vs secondary depression, psychiatric diagnoses other than major depression, other substance use disorders, and the prescription of antidepressants at discharge from the hospital. In the few instances in which subjects were unavailable for follow-up before drinking status was ascertained, we performed each survival analysis twice by assigning the status first as relapsed and second as abstinent. Unless otherwise indicated, data are given as mean±SD.

Women and men differed significantly in the number of years of total alcohol use (t=2.34; df=99; P=.02), with men reporting drinking for 24.9±10.2 years, whereas women reported using alcohol for 20.1±10.3 years. Women and men did not differ significantly in other baseline drinking characteristics or in any ASI subscale scores during the 30 days before hospital admission.

PSYCHIATRIC DISORDERS AND SYMPTOMS

Co-occurring psychiatric disorder diagnoses are summarized in **Table 3**. Among the women with current major depression, 11 (57.9%) had a diagnosis of primary depression, compared with 9 (47.4%) men with current major depression, but this difference was also not statistically significant.

The mean initial BDI score for the total study sample was 17.4±10.1. The mean initial BDI score among those with current major depression was 22.71±9.95 and for those with no current major depression was 14.25±8.91. These scores reflect depressive symptoms of moderate severity.[38] This difference was statistically significant (t=4.421; df=99; $P<.001$). There was no significant difference by sex in initial BDI scores.

SURVIVAL ANALYSIS

We obtained data regarding the length of time to first drink for 93 (92.1%) of 101 subjects; data for time to relapse were obtained for 91 subjects (90.1). Eight of these subjects who were unavailable for follow-up had been abstinent at the time of their last follow-up appointment, and 2 were unavailable after they had returned to drinking but had not met criteria for relapse. We compared the survival analyses in which we coded the subjects who were unavailable for follow-up as relapsed with survival analyses in which we coded these subjects as abstinent. This comparison revealed no significant differences. Therefore, for the purposes of our analyses, those with unknown drinking status were considered to have had a relapse at the time that they were unavailable for follow-up.

Table 1. Sociodemographic Characteristics by Sex and Presence of Current Major Depression*

	Total (N=101)	Women (n=41)	Men (n=60)	Subjects With Current Major Depression (n=38)	Subjects Without Current Major Depression (n=63)
Mean±SD age, y	43.3±11.1	42.0±11.1	44.1±11.1	42.2±10.9	44.0±11.2
Marital status, % of subjects					
Married	41.0	43.9	39.0	34.2	45.2
Separated or divorced	24.0	19.5	27.1	39.5	14.5
Other	35.0	36.6	33.9	26.3	40.3
White subjects, %	94.0	95.1	93.3	92.1	95.2
Education, % of subjects†					
Some college or more	79.2	90.2	71.7	76.3	81.0
High school diploma or less	20.8	9.8	28.3	23.7	19.0
Employment, % of subjects‡					
Employed full-time	41.4	24.4	53.4	31.6	47.5
Disabled or retired	25.3	14.6	32.8	29.0	23.0
Unemployed	15.1	24.4	8.6	21.1	11.5
Other	18.2	36.5	5.2	18.4	18.1

**Unless otherwise indicated, differences are not statistically significant.*
†*For difference by sex,* $\chi^2=5.1$, df=1, $P<.05$.
‡*For difference by sex,* $\chi^2=25.0$, df=3, $P<.001$.

Table 2. Baseline Drinking Characteristics of Subjects With and Without Major Depression*

Drinking Characteristics	Subjects With Major Depression (n=38)	Subjects Without Major Depression (n=63)	All Subjects (N=101)
Age at first alcohol use, y	15.6±5.7	15.4±6.1	15.5±5.9
Alcohol use, y†	20.9±9.1	24.2±11.1	23.0±10.5
Heavy alcohol use, y‡	10.1±7.8	12.1±8.0	11.4±8.0
No. of drinking days in 30 days before admission	19.6±9.4	18.2±9.9	18.7±9.7
No. of drinks per drinking day in 30 days before admission	13.3±6.2	12.6±7.2	12.8±6.8
Age at first alcohol or other drug treatment, y	34.5±10.4	38.1±11.7	36.8±11.3
No. of previous detoxifications§	10.1±22.7	6.2±18.5	7.7±20.1
No. of detoxifications in previous year‖	1.3±2.1	1.1±2.2	1.2±2.2

**Unless otherwise indicated, differences are assessed using the* t *test. None of these differences is statistically significant. Data are given as mean±SD.*
†*Difference was assessed using Cochran-Mantel-Haenszel trend test. Groups were 0 to 7, 8 to 21, 22 to 29, and 30 or more years of alcohol use (*P=.70).
‡*Difference was assessed using Cochran-Mantel-Haenszel trend test. Groups were 0 to 4, 5 to 9, 10 to 19, and 20 or more years of heavy alcohol use (*P=.19).
§*Difference was assessed using Cochran-Mantel-Haenszel trend test. Groups were 0, 1, 2, and more than 2 detoxifications (*P=.39).
‖*Difference was assessed using Cochran-Mantel-Haenszel trend test. Groups were 0, 1, 2, and more than 2 detoxifications (*P=.09).

Table 3. Current *DSM-III-R* Diagnoses Assessed During Hospitalization*

	% of Subjects		
Diagnoses	Men (n=60)	Women (n=41)	All Subjects (N=101)
Major depression†	31.7	46.3	37.6
Other mood disorders (excluding major depression)	13.3	14.6	13.9
Anxiety disorders‡	18.3	34.1	24.8
Antisocial personality disorder§	10.0	0	5.9
Other substance use disorder	10.0	14.6	11.9
Any psychiatric diagnosis (other than alcohol dependence)	51.7	65.9	57.4

**Differences were tested using* χ^2 *test. Unless otherwise indicated, difference is not statistically significant.*
†*Thirty-four of 38 patients with major depression met full criteria at time of admission. Four of 38 patients met full criteria within 6 months and met 4 of 9 criteria at the time of admission (eg, major depression in partial remission).*
‡*Anxiety disorders included are general anxiety disorder, panic disorder, agoraphobia, simple phobia, and social phobia.*
§*Fisher exact test indicates a trend toward significance (*P=.08).

When depression was measured symptomatically by initial BDI score, there was no relationship between depressive symptoms and time to first drink or relapse. However, a *DSM-III-R* diagnosis of major depression was significantly related to both times to first drink and relapse. The presence of current major depression was significantly related to time to first drink with a hazard ratio of 2.03 (95% confidence interval [CI], 1.28-3.21; *P*=.003). Adjustment of the Cox model for the independent variables marital status, education, and employment (all pre-

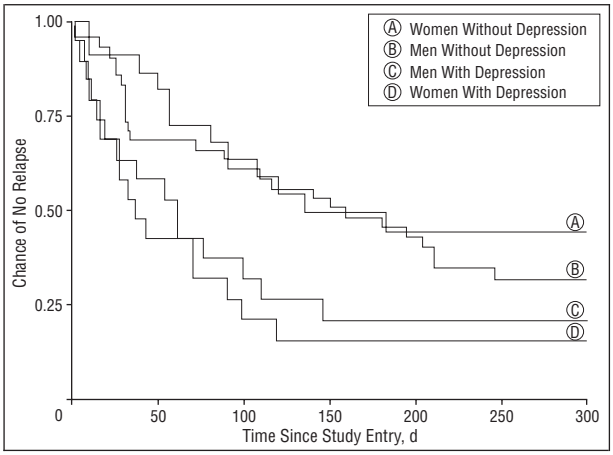

Figure 1. *Depression and sex as predictors of time to relapse. Depression indicates a* DSM-III-R *diagnosis of current major depression; relapse, 3 or more standard drinks on a drinking day for women and 5 or more standard drinks on a drinking day for men.*

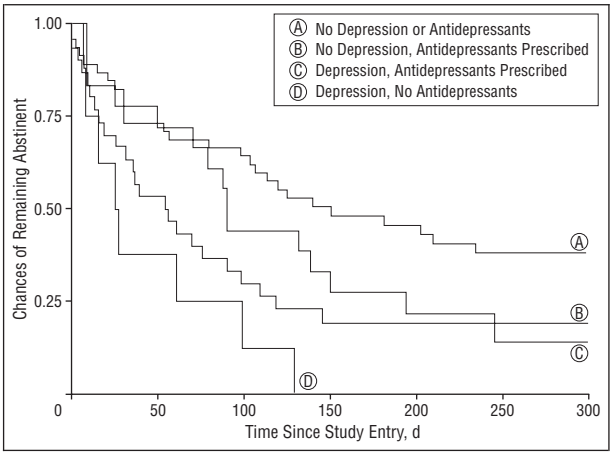

Figure 2. *Relation of depression and antidepressants at hospital discharge to time to first drink. Depression indicates a* DSM-III-R *diagnosis of current major depression.*

viously shown to influence outcome in alcohol dependence[18,34]) demonstrated that baseline major depression remained significantly related with a hazard ratio of 2.07 (95% CI, 1.29-3.33; P=.002). Sex was not significantly related to return to drinking, and there was no significant interaction of sex with major depression. Median times of return to drinking were 125 and 38 days, respectively, for nondepressed and depressed subjects.

As shown in **Figure 1**, the presence of current major depression was also significantly related to time to relapse, with a hazard ratio of 2.12 (95% CI, 1.32-3.39; P=.002). Sex was not significantly related to time to relapse, and there was no significant interaction between depression diagnosis and sex. When the hazard ratio was adjusted for education, marital status, and employment, it was 2.26 (95% CI, 1.39-3.68; P<.001). Nondepressed and depressed subjects had median relapse times of 150 and 41 days, respectively. Interestingly, Kaplan-Meier estimates of the proportions of nondepressed and depressed subjects remaining abstinent throughout follow-up were 32.3% and 12.6%, respectively (SE=0.0600 and 0.0551; z=2.417; P=.02).

To assess the impact of differentiating primary vs secondary depression, we controlled for this distinction in a separate survival analysis. There was no statistically significant difference in time to first drink or relapse for subjects with primary vs secondary depression, but each differed significantly from those with no depression (P=.003 and P=.05, respectively).

Of 38 subjects with current major depression, 30 (15 men and 15 women [78.9%]) were prescribed antidepressants at hospital discharge. Of 63 subjects without current depression, 19 (11 men and 8 women [30.2%]) were prescribed antidepressants at discharge for an anxiety or other disorder. **Figure 2** presents the relationship among use of antidepressants at discharge, current major depression at baseline, and time to first drink. Again, current major depression was significantly related to a shorter time to first drink (hazard ratio, 2.01; 95% CI, 1.15-3.52; P=.01). Time to first drink was significantly longer for those without current depression, regardless of prescription of antidepressants at discharge. However, among those with major depression, time to first drink was slightly longer for those who were discharged receiving antidepressants. By day 100, virtually all depressed subjects who were discharged without antidepressants had returned to drinking, whereas 20% of those who were depressed and discharged receiving antidepressants remained abstinent at 1 year.

In a separate survival analysis, a baseline psychiatric diagnosis other than major depression or substance use disorder was not significantly associated with time to first drink. However, the presence of another substance use disorder at baseline was significantly associated with time to first drink (hazard ratio, 2.58; 95% CI, 1.37-4.83; P=.003). We performed a separate Cox proportional hazards model for baseline depression diagnosis and entered presence of another substance use diagnosis at baseline as a control variable. We found that the main effect of baseline depression on time to first drink remained significant with a hazard ratio of 1.87 (95% CI, 1.17-2.99; P=.009). There was no interaction between the effects of these 2 diagnoses and time to first drink.

VALIDITY OF SELF-REPORTS OF ALCOHOL CONSUMPTION

Ninety-four (93.1%) of the 101 subjects designated a collateral informant. We tried to contact each informant within 1 week of the subject's monthly follow-up visit, and were able to do so 65% of the time. Self-reports of drinking and abstinence correlated significantly with reports of the collateral informants (κ=0.69; P<.001). In only 18 (3.2%) of 554 informant reports did an informant say that a subject had been drinking when the subject reported abstinence. This correlation compares favorably with previously published validation data.[49]

COMMENT

We found that a diagnosis of current major depression at the time of hospitalization for detoxification was significantly related to times to first drink and relapse for men and women, regardless of whether major depres-

sion was primary or secondary. These findings differ from those of Rounsaville et al,[4] in which drinking outcomes at 1 year were better for depressed women but worse for depressed men.

Our findings may differ from those of previous studies[4,22] because our study investigated the relationship of a *DSM-III-R* diagnosis of current major depression with times to first drink and relapse, whereas previous studies[4,22] have examined the relationship of a lifetime diagnosis of major depression to frequency and intensity of drinking at 1 year. The presence of a current disorder may be more informative regarding the short-term consequences of alcohol dependence.[26] Unfortunately, we did not have a sufficient number of subjects who met criteria for lifetime, but not current, major depression to assess the significance of difference between lifetime and current diagnoses on return to drinking.

Another factor that may explain the lack of a sex difference in our study is the striking similarity between women and men with respect to the relative prevalence of co-occurring psychiatric diagnoses and drinking histories. The lack of a sex difference in the prevalence of co-occurring mood disorders in our study sample is consistent with other alcohol treatment–seeking samples[45] but differs from national community samples in which women with[3] and without[55] alcohol dependence are more likely to have co-occurring depression. The similarity in the severity of men's and women's alcohol dependence despite the longer duration of drinking in men is consistent with previous research.[56-58] This gender similarity may also be consistent with purported national trends of increased heavy drinking in more recent cohorts of women[59] or a recent secular trend in which hospitalization for alcohol dependence has become restricted to those most severely affected by their alcohol dependence.[60]

Our results indicate that although symptoms of depression per se do not predict drinking outcomes, depression that is defined by diagnostic criteria is associated with more rapid relapse for men and women. This result suggests that depression as defined by diagnostic criteria represents a more enduring condition than depressive symptoms that may be substance induced and transient[7,11] or may represent dsyphoria that is unrelated to depressive disorder and nonresponsive to antidepressant therapy.[19,20] In addition, depressive symptoms per se may be less likely to discriminate between substance- vs depression-induced symptoms. For example, the BDI contains a question about the amount of time that the subject feels guilty. Although feeling guilty may be part of a depressive syndrome, it is also used as a screening question for alcohol abuse and dependence.[61]

Although patients with coexisting psychiatric illness and substance use disorders have traditionally had poor outcomes,[62] recent studies of concurrent treatment of both disorders have demonstrated more favorable outcomes.[63] Successful concurrent treatment depends on accurate diagnosis, and the question of when a valid diagnosis of major depression can be made in a patient with alcohol dependence has been controversial.[43,47] In our study, however, a diagnosis of current major depression at the time of treatment entry predicted a more rapid return to drinking for men and women, even when no attempt was made to exclude potential substance-induced symptoms.

Because our study was not a controlled intervention study, we did not specifically monitor antidepressant therapy adherence; nevertheless, it is significant that depressed patients who received antidepressants at hospital discharge returned to drinking more slowly than those who received no medication. These data suggest that simultaneous treatment of concurrent major depression and alcohol dependence improves drinking outcomes. This finding is consistent with those of 2 recent placebo-controlled trials of antidepressants in individuals with alcohol dependence and major depression.[63,64] To our knowledge, our study is the first noncontrolled, naturalistic study of treatment-seeking patients with alcohol dependence that shows similar results to these placebo-controlled trials.[63,64]

Our study has a number of limitations. It is unclear, for instance, to what extent our results are generalizable, since our population may have different sociodemographic characteristics and more comorbid psychiatric illness than other treatment-seeking populations in the community. Another limitation is that we did not specifically examine any particular intervention or control for ongoing treatments during follow-up. In some instances, small numbers of subjects may have limited our ability to detect differences between groups, such as those with primary vs secondary depression.

These results support previous work demonstrating that a careful psychiatric diagnostic assessment is necessary to provide optimal treatment for alcohol-dependent patients. Future analyses examining the interaction of major depression and drinking behavior during follow-up in this and other populations may yield important information about the natural course of illness and treatment response in men and women.

Accepted for publication August 18, 1997.

Supported by grant AA 09881 from the National Institute on Alcohol Abuse and Alcoholism, Bethesda, Md (Dr Greenfield); by grants DA 09400 (Drs Greenfield and Weiss), DA 07252 (Dr Greenfield), and DA00326 (Dr Weiss) from the National Institute on Drug Abuse, Rockville, Md; and by the Dr Ralph and Marian C. Falk Medical Research Trust, Chicago, Ill (Drs Greenfield and Weiss).

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