Course of Late-Life Depression With Alcoholism Following Combination Therapy*

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ABSTRACT. Objective: The comorbidity of alcoholism and depression increases the complexity of treatment and is associated with severe disability and morbidity. However, long-term treatment algorithms have been understudied. **Method:** This study examined the natural course of 74 depressed alcoholics over 6 to 12 months following a 12-week acute-phase trial of sertraline (Zoloft), naltrexone (Revia), and compliance enhancement therapy. Subjects were monitored for long-term outcomes based on their acute-phase trial response. **Results:** Fifty-four subjects followed up at 6 months, and 50 subjects remained at the 12-month visit. Full responders at the end of the 12-week acute-phase trial sustained better overall outcomes (6 months: $\chi^2 = 19.9$, 4 df, $p = .001$; 12 months: $\chi^2 = 11.7$, 4 df, $p = .020$) and better drinking and depression outcomes, as compared with partial responders and nonresponders over a 6-month and 12-month period. **Conclusions:** Initial full responders sustain better overall treatment outcomes at 6 and 12 months, compared with partial responders and nonresponders. The defined outcome categories incorporate meaningful and practical measures of severity and can help predict treatment outcomes in clinical practice, thereby allowing timely interventions. Future studies should focus on maintenance strategies for full responders and treatment adaptations for partial responders and nonresponders. (*J. Stud. Alcohol Drugs* **70:** 237-241, 2009)

THE COMORBIDITY OF alcoholism and depression is very prevalent (Hasin, 2005; Kessler, 2003) and is associated with high severity (Burns et al., 2005), high costs (Fortney et al., 1999), and poor functional prognosis (Blixen et al., 1997). Although cause and effect are difficult to establish, depressive symptoms typically predict increased alcohol use (Driessen et al., 2001; Hasin, 2002; Kranzler et al., 1996). Conversely, relapse to heavy drinking predicts poor response to depression treatment (Nunes and Levin., 2004; Oslin, 2005; Wagner et al., 2004).

Although depressed alcoholics with complex treatment regimens are routine in clinical practice, they often are excluded in research settings (Oslin, 2005). Generally, antidepressants have poor (Gual et al., 2003; Kranzler et al., 1995, 2006) to modest (Nunes and Levin, 2004) benefits related to drinking behaviors. Likewise, anti-alcohol agents such as naltrexone (Revia) or disulfiram (Antabuse) have little impact on depression outcomes (Petrakis et al., 2007). Controlled studies in depressed alcoholics employing combinations of antidepressants and anti-alcohol agents are few (Borup and Unden, 1994), and currently no empirically proven treatment exists for that population (Cornelius et al., 2003). Thus, there is a need for combination-therapy trials in dually diagnosed subjects. In a 12-week double-blind, randomized, controlled trial of older depressed alcoholics, we found no evidence for an added benefit of naltrexone in combination with sertraline (Zoloft) and compliance enhancement therapy (Oslin, 2005). That study also demonstrated general overall benefits, with 42% of all subjects experiencing a remission in depression without relapse to heavy drinking. In another 14-week comorbidity study conducted at the same center, 170 depressed alcoholics ages 20-73 years were randomized to sertraline (200 mg/day), naltrexone (100 mg/day), the combination, or placebo, with everyone receiving cognitive-behavioral

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therapy. More patients treated with the sertraline-naltrexone combination achieved abstinence while in treatment and remained nondepressed by the end of treatment than patients treated with placebo or either medication alone (H.M. Pettinati, personal communication, April 6, 2008).

The chronic course of alcohol-depression comorbidity necessitates long-term follow-up. Prognostic studies in geriatric populations following combination regimens have been surprisingly lacking. One study that examined a 1-year naturalistic course of middle-age depressed alcoholics on a combination of fluoxetine (Prozac) and disulfiram reported a vaguely defined *good clinical outcome* among 70% of the subjects (Borup and Unden, 1994). Clear definitions of *recovery* among dually diagnosed patients thus have been remarkably missing. The aim of this article was to examine the stability of treatment outcomes achieved in our 12-week acute-phase trial in the elderly during naturalistic follow-up at 6 and 12 months. We hypothesized that subjects who achieved remission in depression and did not relapse to heavy drinking at the end of the 12-week acute-phase trial would sustain better overall treatment outcomes at the 6- and 12-month follow-up visits, as compared with those who remained depressed and/or relapsed to heavy drinking (at the end of the 12-week trial).

Method

Participants

Seventy-four consenting outpatients enrolled from 1999 to 2001 in the University of Pennsylvania Institutional Review Board–approved acute-phase trial. Subjects were 55 years or older and met criteria for alcohol dependence and depressive disorder (substance induced or primary major depression) according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (American Psychiatric Association, 1994). Subjects were excluded if they met criteria for any psychoactive substance dependence besides alcohol or nicotine or if they had a severe medical illness.

Treatment conditions

In the original acute-phase trial, subjects were randomly assigned to 12 weeks of naltrexone (Revia; 50 mg/day) or placebo, with all subjects receiving sertraline (100 mg/day) and compliance enhancement therapy (Oslin, 2005). At the conclusion of the trial (12-week visit), subjects were reassessed, and treatment was facilitated. They were encouraged to continue treatment with self-help groups and medications and were asked to followup at 6 and 12 months (calculated from the time of intake) under open-label conditions. At these visits, verifiable information was gathered on their drinking and depression.

Assessments

The measures administered at the 6- and 12-month visits included the Hamilton Rating Scale for Depression (HAM-D) to measure depression responses (Hamilton, 1960) and the Timeline Followback (TLFB) to assess the frequency and quantity of alcohol use (Sobel and Sobel, 1992). We examined three posttrial compliance scenarios (i.e., compliance with self-help groups, naltrexone, and antidepressants) that could influence overall outcomes at 6 and 12 months. Information on treatment adherence was obtained from patient self-report.

Outcome measures

For purposes of standardization, all outcomes were based on subject information for the 30 days preceding the 12-week, 6-month, and 12-month visits. Subjects were divided into three groups based on composite scores of their drinking and depression outcomes at the 12-week visit. The groups were defined as (1) full responders: subjects who had depression remission (HAM-D < 10) and no relapse to heavy drinking; (2) partial responders: subjects who either were depressed (HAM-D ≥ 10) or relapsed to heavy drinking but not both; and (3) nonresponders: subjects who were depressed (HAM-D ≥ 10) and relapsed to heavy drinking. The HAM-D cutoff score of 10 was based on current geriatric literature (Taylor et al., 2004). *Relapse to heavy drinking* was defined as more than four standard drinks per day for men and more than three standard drinks per day for women (Sanchez-Craig, 1995).

The primary outcomes were categories based on a composite of TLFB and HAM-D scores at 6 and 12 months (i.e., full responders, partial responders, and nonresponders, grouped by identical definitions used at the 12-week visit). The secondary outcome variables included indexes of drinking and depression. The drinking indexes derived from TLFB included relapse to heavy drinking, proportion of heavy drinking days, total drinks per heavy drinking day, complete abstinence from drinking, total days of drinking, total number of drinks, proportion of drinking days, and total drinks per day. The depression index included total depression scores on HAM-D.

Statistical analysis

Statistical analysis was performed using Windows SPSS (Version 15; SPSS Inc., Chicago, IL) and was restricted to the subjects whose complete information was available at 6- and 12-month follow-up. Descriptive analysis included means and standard deviations for continuous measures and frequencies for categorical measures. Group comparisons for outcome measures were conducted using analysis of variance (ANOVA) for continuous measures and chi-square tests for

categorical measures. Analysis was adjusted to control for multiple comparisons using Bonferroni correction. The post-trial follow-up scenarios were classified into categories, and chi-square tests were used to test for associations.

Results

Subject retention and demographics

A majority of the subjects were white (72.2%) and male (79.6%), averaging 63.4 years. Of the 74 subjects who enrolled in the acute-phase trial, 54 completed the 6-month visit (13 were lost to follow-up; 7 had incomplete data), and 50 completed the 12-month visit (4 more were lost to follow-up).

There were no differences between the participants at 6- and 12-month follow-up or between participants and treatment dropouts on any demographic variables (age, gender, marital status, race, or religion). Furthermore, there were no demographic differences between full responders, partial responders, and nonresponders.

Overall outcomes

Full responders at 12 weeks sustained better overall treatment outcomes at 6 months ($\chi^2 = 19.9$, 4 df, $p = .001$) and 12 months ($\chi^2 = 11.7$, 4 df, $p = .02$), compared with partial responders and nonresponders. The association was significant even when the groups were divided using more stringent alcohol outcome criteria—that is, complete abstinence (6 months: $\chi^2 = 20.84$, 4 df, $p < .0001$; 12 months: $\chi^2 = 12.50$, 4 df, $p < .05$).

Drinking outcomes

As seen in Table 1, full responders maintained significant improvements on drinking measures such as relapse to heavy drinking, proportion of heavy drinking days, and drinks per heavy drinking day at 6- and 12-month follow-up. Additionally, they maintained similar improvements with regard to complete abstinence (6 months: $\chi^2 = 20.9$, 2 df, $p = .000$; 12 months: $\chi^2 = 14.4$, 2 df, $p = .001$), total days of drinking (6 months: $F = 6.2$, 2 df, $p = .004$; 12 months: $F = 3.5$, 2 df, $p = .039$), total number of drinks (6 months: $F = 4.4$, 2 df, $p = .017$; 12 months: $F = 6.4$, 2 df, $p = .003$), proportion of drinking days (6 months: $F = 6.2$, 2 df, $p = .004$; 12 months: $F = 3.4$, 2 df, $p = .043$), and total drinks per day (6 months: $F = 4.4$, 2 df, $p = .017$; 12 months: $F = 6.3$, 2 df, $p = .004$) at the 6- and 12-month follow-up.

Depression outcomes

As seen in Table 1, the depression outcomes (both rates and severity of depression) were sustained better among the

Table 1. Outcomes at 6-month and 12-month follow-up

	6-month outcomes					12-month outcomes				
		Groups based on categorical outcomes at the end of active trial at 12 weeks					Groups based on categorical outcomes at the end of active trial at 12 weeks			
Variable	Overall ($N = 54$)	Full resp. ($n = 25$)	Partial resp. ($n = 22$)	Nonresp. ($n = 7$)	Statistic and signif.	Overall ($N = 50$)	Full resp. ($n = 22$)	Partial resp. ($n = 21$)	Nonresp. ($n = 7$)	Statistic and signif.
Overall outcomes										
% full responders	40.7%	68.0%	13.6%	28.6%	$\chi^2 = 19.9$, 4 df, $p = .001$[a]	42.0%	63.6%	33.3%	0.0%	$\chi^2 = 11.7$, 4 df, $p = .020$[a]
Drinking outcomes										
% Relapsed to heavy drinking	38.9%	12.0%	59.1%	71.4%	$\chi^2 = 14.5$, 2 df, $p = .001$[a]	34.0%	18.2%	28.6%	100%	$\chi^2 = 16.3$, 2 df, $p < .001$[a]
Proportion of heavy drinking days	0.1 (0.3)	0.0 (0.2)	0.1 (0.2)	0.4 (0.4)	$F = 8.2$, 2 df, $p = .001$	0.2 (0.3)	0.1 (0.3)	0.1 (0.2)	0.5 (0.4)	$F = 7.04$, 2 df, $p = .002$
Drinks per heavy drinking day	3.5 (5.6)	0.8 (1.7)	5.7 (7.4)	6.0 (4.4)	$F = 6.1$, 2 df, $p = .004$	2.9 (4.0)	1.5 (2.4)	2.0 (3.0)	9.9 (3.8)	$F = 24.38$, 2 df, $p < .001$
Depression outcomes										
% Depressed (HAM-D ≥ 10)	46.3%	24.0%	68.2%	57.1%	$\chi^2 = 9.6$, 2 df, $p = .008$[a]	40.0%	27.3%	52.4%	42.9%	$\chi^2 = 2.85$, ns
HAM-D scores	11.1 (7.3)	7.1 (5.4)	14.7 (6.8)	14.1 (8.3)	$F = 9.2$, 2 df, $p < .001$	11.8 (9.1)	8.8 (7.0)	14.2 (9.9)	14.3 (10.8)	$F = 2.37$, ns

Notes: For categorical variables, frequencies are shown in percentages. For continuous variables, values are shown as mean (SD). All outcomes based on information obtained for 30 days before the 12-week, 6-month, and 12-month visit. Resp. = responders; nonresp. = nonresponders; signif. = significance; HAM-D = Hamilton Rating Scale for Depression; ns = not significant. [a]Indicates that certain individual cells had numbers less than the minimum required for chi-square analysis.

full-responder group. These findings were statistically significant at 6 months but not at 12 months. The depression outcomes among the partial responders and the nonresponders looked interestingly similar.

Impact of posttrial compliance

The posttrial compliance scenarios—that is, attendance at support-group meetings and compliance with naltrexone and antidepressants—were expected to have significant effects on the outcomes. None of them, however, played a role in the overall outcomes at 6 and 12 months. The overall compliance was encouraging, with the majority continuing naltrexone (73%) and an antidepressant (84% with 60.4% continuing sertraline) at 6 months. At the 12-month visit, 40% complied with naltrexone, and 69.4% continued on an antidepressant (44.9% on sertraline).

Discussion

Results from the analysis confirm the hypothesis that full responders at the end of the 12-week acute-phase trial sustain better overall treatment outcomes at 6 and 12 months, compared with partial responders and nonresponders. These associations hold true even with a stricter definition of *drinking recovery* (i.e., abstinence). The associations are robust when individual drinking measures are examined across the groups at 6- and 12-month visits. The weak sustainability of depression outcomes is consistent with findings elsewhere (Cornelius et al., 2005) and could be attributed to the refractory nature of depression (Nunes, 2004).

Interestingly, there seem to be different factors driving the course of recovery. A majority of the full responders maintained depression recovery (>70%, with average HAM-D scores ranging from 7 to 9) and sobriety (>80%) at 6 and 12 months. Thus, the course among the full responders appears to be driven by well-maintained depression outcomes as well as good drinking outcomes. In contrast, the poor outcomes among the nonresponders appear to be driven by poor drinking recovery, with more than 71% of the nonresponders continuing to drink at 6 months and all of the nonresponders continuing to drink at 12 months. The depression outcomes in that group were comparable to the depression outcomes of the entire sample. As expected, the picture is blurred in the partial-responder group, with both depression and drinking failures equally responsible for poor outcomes at 6 and 12 months.

There was no impact of posttrial compliance on the course of recovery. Despite a substantial drop in naltrexone compliance between 6 and 12 months, corresponding overall sobriety rates are encouraging, possibly suggesting residual benefits. However, these findings should be taken in the context of the acute-phase trial, where naltrexone conferred little benefit over placebo and sertraline probably had some modest benefits on the overall drinking outcomes (Moak et al., 2003). In contrast, there seems to be a different story concerning depression recovery. Despite a relatively high antidepressant compliance rate, more than 45% of the subjects were depressed at 6 and 12 months, indicating limited benefits. Perhaps this result suggests that close attention should be paid to nonrecovering dual-diagnosed subjects and that their depression should be treated aggressively.

The limitations of the study included a small sample size, high attrition rates in the follow-up population, lack of control on the follow-up compliance scenarios, limited representation of women, and a restricted age range. In addition, we assumed that the information obtained from subjects in the 30 days preceding the 6- and 12-month follow-up reflected their overall status during the entire period.

The design of the trial and the naturalistic follow-up make it quite relevant to the comorbid and geriatric population where complexities and chronicity are routine. The outcome categories incorporate meaningful and practical measures (i.e., TLFB and HAM-D). The suggested outcome categories could plausibly fill in the knowledge gap pertaining to definitions of recovery in dually diagnosed patients. By examining clinical prognosis in these outcome categories in further trials, we can help derive timely interventions. Future studies should focus on maintenance strategies for full responders and treatment adaptations for partial responders and nonresponders.

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