Combined Pharmacotherapies and Behavioral Interventions for Alcohol Dependence

The COMBINE Study: A Randomized Controlled Trial

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A BOUT 8 MILLION INDIVIDUALS IN the United States currently meet diagnostic criteria for alcohol dependence, a leading preventable cause of morbidity and mortality and a major contributor to health care costs. In primary care settings, the prevalence of alcohol use disorders ranges from 20% to 36%; most of those patients are never treated and, if they are

Context Alcohol dependence treatment may include medications, behavioral therapies, or both. It is unknown how combining these treatments may impact their effectiveness, especially in the context of primary care and other nonspecialty settings.

Objectives To evaluate the efficacy of medication, behavioral therapies, and their combinations for treatment of alcohol dependence and to evaluate placebo effect on overall outcome.


Interventions Eight groups of patients received medical management with 16 weeks of naltrexone (100 mg/d) or acamprosate (3 g/d), both, and/or both placebos, with or without a combined behavioral intervention (CBI). A ninth group received CBI only (no pills). Patients were also evaluated for up to 1 year after treatment.

Main Outcome Measures Percent days abstinent from alcohol and time to first heavy drinking day.

Results All groups showed substantial reduction in drinking. During treatment, patients receiving naltrexone plus medical management (n=302), CBI plus medical management and placebos (n=305), or both naltrexone and CBI plus medical management (n=309) had higher percent days abstinent (80.6, 79.2, and 77.1, respectively) than the 75.1 in those receiving placebos and medical management only (n=305), a significant naltrexone \times behavioral intervention interaction (P=.009). Naltrexone also reduced risk of a heavy drinking day (hazard ratio, 0.72; 97.5% CI, 0.53-0.98; P=.02) over time, most evident in those receiving medical management but not CBI. Acamprosate showed no significant effect on drinking vs placebo, either by itself or with any combination of naltrexone, CBI, or both. During treatment, those receiving CBI without pills or medical management (n=157) had lower percent days abstinent (66.6) than those receiving placebo plus medical management alone (n=153) or placebo plus medical management and CBI (n=156) (73.8 and 79.8, respectively; P<.001). One year after treatment, these between-group effects were similar but no longer significant.

Conclusions Patients receiving medical management with naltrexone, CBI, or both fared better on drinking outcomes, whereas acamprosate showed no evidence of efficacy, with or without CBI. No combination produced better efficacy than naltrexone or CBI alone in the presence of medical management. Placebo pills and meeting with a health care professional had a positive effect above that of CBI during treatment. Naltrexone with medical management could be delivered in health care settings, thus serving alcohol-dependent patients who might otherwise not receive treatment.

Trial Registration clinicaltrials.gov Identifier: NCT00006206

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similar to those represented in general population care, do not receive specialty care (National Institute on Alcohol Abuse and Alcoholism [NIAAA], unpublished data).8 Primary care physicians can play a significant role in addressing alcohol use disorders.3,7 It is of interest whether medications for alcoholism are efficacious without specialist intervention and whether efficacy can be improved by combining different medications with or without specialist care. These questions are particularly important given that most problem drinkers are seen in health care settings, rather than in specialist treatment programs. The Combined Pharmacotherapies and Behavioral Interventions (COMBINE) Study was designed to address these issues.

Several behavioral treatments9-11 and at least 2 medications approved by the US Food and Drug Administration, naltrexone and acamprosate,12-15 have shown efficacy in the treatment of alcohol dependence. However, no large-scale randomized controlled study has evaluated whether combined pharmacotherapy with or without behavioral therapy could improve outcome. For example, it is unclear16 whether combining naltrexone (an opiate receptor antagonist) with acamprosate (a putative glutamate modulator)17-19 is superior to monopharmacotherapy, with or without additional behavioral therapy. At the time of initiation of this study, acamprosate was approved in Europe but was still an investigational drug in the United States. Although naltrexone was approved in the United States, evidence of its efficacy was primarily based on small single-site studies using specialist models of treatment. Multisite studies have yielded conflicting results.20,21 Thus, assessing the efficacy of each of these medications, alone and combined, in a large multisite trial was of interest. Sponsored by the NIAAA, this multisite, randomized, controlled trial evaluated medical management with naltrexone, acamprosate, or both, with or without additional specialist treatment (combined behavioral intervention [CBI]).

In addition, there is no solid information on how well alcohol-dependent individuals will respond solely to the act of pill taking and being counseled by a health care professional. A secondary aim of this study was to evaluate whether taking placebo pills and being seen regularly by a health care professional would enhance addiction specialist counseling. A final goal was to evaluate if improvements observed over 16 weeks of treatment would be maintained for up to 1 year after treatment ended.

**METHODS**

**Overview of Study Design**

The COMBINE Study rationale, design, and methods have been previously detailed.22,23 In brief, after baseline assessment and attainment of 4 days of abstinence, 1383 eligible alcohol-dependent individuals were randomly assigned to 1 of 9 groups for 16 weeks of outpatient treatment (Figure 1). Eight of these groups (n=1226) received medical management, a 9-session intervention focused on enhancing medication adherence and abstinence using a model that could be adapted by primary care settings. Four of these groups (n=619) also received more intensive counseling (CBI) delivered by alcoholism treatment specialists. Patients in all 8 groups received either active/placebo naltrexone or active/placebo acamprosate, yielding 4 medication conditions (placebo, acamprosate, naltrexone, and acamprosate plus naltrexone) within each level of behavioral counseling (CBI vs no CBI). A ninth group (n=157) received CBI alone, without pills or medical management, and was included to address the separate question of placebo effects. The protocol specified that all individuals should be assessed 9 times during the 16 weeks of treatment and at 26, 52, and 68 weeks after randomization, ie, up to 1 year after treatment ended.

**Recruitment and Randomization**

Participants were recruited by advertisements and from clinical referrals at 11 academic sites. Approximately 5000 potential participants were screened by telephone or in person.22 All participants seen in person signed an informed consent form approved by each site’s institutional review board, accompanied by a certificate of confidentiality issued by the NIAAA. Baseline drinking histories, psychosocial data, health screens (including laboratory general health panels), and levels of specific alcohol biomarkers were obtained, totaling about 4.5 hours.

Eligibility criteria included (1) alcohol dependence, determined by Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)24 criteria, using the Structured Clinical Interview for DSM-IV25; (2) 4 to 21 days of abstinence; and (3) more than 14 drinks (women) or 21 drinks (men) per week, with at least 2 heavy drinking days (defined as ≥4 drinks/d for women and ≥5 drinks/d for men) during a consecutive 30-day period within the 90 days prior to baseline evaluation. Exclusion criteria included (1) history of other substance abuse (other than nicotine or cannabis) by DSM-IV criteria in the last 90 days (6 months for opiate abuse) or by urine drug screen, (2) psychiatric disorder requiring medication, or (3) unstable medical conditions (eg, serum liver enzyme levels >3 times the upper limit of normal). Eligible participants were randomly assigned to treatments using a permuted block design, using blocks of 9, stratified by site. The randomization was implemented via a central telephone-based interactive voice response system at the coordinating center.

**Assessment**

Drinking parameters obtained from structured interviews at baseline26,27 and during the 16-week treatment period28 are the main focus of this report. A secondary analysis of drinking parameters in the 1 year after treatment is also presented. At the 9 medical management visits (except for the CBI no pill/no medical management group) during treatment (see below), research assistants (not blinded to, or providing, psychosocial treatment) assessed alcohol consumption29 and craving30,31 Two-
hour assessments were performed at weeks 8 and 16 during treatment and again at postrandomization weeks 26, 52, and 68 (1 year posttreatment) during follow-up. Adverse medication effects were assessed by a health care professional at each appointment using the Systematic Assessment for Treatment Emergent Effects (SAFTEE) interview. A complete blood cell count and liver and kidney function tests were performed at baseline and every 4 weeks. Levels of γ-glutamyltransferase and percent carbohydrate-deficient transferrin (%CDT) were measured at baseline and at weeks 8 and 16. For the CBI no pill/no medical management group, assessments were made by research assistants at the same postrandomization time points as for the other 8 groups.

Race/ethnicity data were collected in compliance with National Institutes of Health guidelines and self-designated by participants, using an item allowing open-ended responses. For this report, responses were categorized as black, Hispanic, non-Hispanic white, or other. Race/ethnicity was not used in analyses of outcomes. However, exploratory analyses will evaluate racial factors, eth-

**Figure 1. Study Profile**

### Volunteers Seeking Treatment for Alcohol Dependence Screened by Telephone for Eligibility

- 4965 Volunteers Seeking Treatment
- 3982 Excluded/Did Not Meet All Eligibility Criteria
- 2928 Excluded at Telephone Screening
- 654 Excluded at Baseline Screening
- 1383 Randomized

### Treatment Groups

- **Placebo**
  - 153 Placebo
  - 153 Attended 1 Visit
- **Acamprosate**
  - 152 Acamprosate
  - 152 Attended 1 Visit
- **Naltrexone**
  - 154 Naltrexone
  - 154 Attended 1 Visit
- **Acamprosate and Naltrexone**
  - 148 Acamprosate and Naltrexone
  - 148 Attended 1 Visit

### Treatment Discontinuation

- 46 Medication Only
  - 35 MM + Medication (All Treatment)
    - 66 Medication
      - 39 MM + Medication (All Treatment)
  - 2 Adverse Events
    - 1 Heavy Drinking
    - 8 Other
  - 3 Lost to Follow-up

### Reasons for Follow-up

- 97 Included in Percent Days Abstinent Analysis
  - 148 Included in Percent Days Abstinent Analysis
    - 154 Included in Percent Days Abstinent Analysis
    - 148 Included in Percent Days Abstinent Analysis
  - 151 Included in Percent Days Abstinent Analysis
    - 155 Included in Percent Days Abstinent Analysis
    - 151 Included in Percent Days Abstinent Analysis
    - 155 Included in Percent Days Abstinent Analysis

**CBI** indicates combined behavioral intervention.

*A patient could discontinue 1 portion of treatment while remaining in another portion (eg, if a patient was assigned to MM plus CBI and he/she discontinued study medication, that patient could continue to attend visits and CBI visits). However, patients who discontinued medical management did not receive further medication.

†Staff could indicate multiple reasons for withdrawal.

‡Patients who did not have a drinking assessment at the end of treatment were categorized as lost to follow-up.

§Patients with no postrandomization drinking data were excluded from the percent days abstinent analysis. In the analysis of relapse to heavy drinking, they were assumed to have relapsed as of their last contact date.
nic factors, or both, as predictors of treatment response in the future. All study site personnel, including investigators, research staff, evaluators, health care (medical management) practitioners, and CBI therapists were blinded to medication assignment, as were participants, through the end of the treatment and the 1-year posttreatment assessment period.

Treatment Conditions

Medications. Each participant in the pill-taking groups was assigned a uniquely numbered medication pack (blister cards) and took up to 8 pills of active medication or placebo daily for 16 weeks. All naltrexone and placebo pills, and all acamprosate and placebo pills, were identical in appearance. Participants in each group took the same number of pills per day. Naltrexone or its placebo was given once per day as 2 pills (1 placebo and 1 pill containing 25 mg or placebo on days 1 through 4, 1 placebo and 1 pill containing 50 mg or placebo on days 5 through 7, and two 50-mg pills [100 mg daily] or placebo on days 8 through 112). Acamprosate or its placebo was administered as 2 pills (500 mg each of acamprosate or placebo) 3 times per day (ie, 3 g daily). Naltrexone and its placebo differed in appearance from acamprosate and its placebo. Based on tolerability, the medical management clinician could reduce the acamprosate pills and then reduce the naltrexone pills. Attempts were made to reestablish the full dose. Doses were chosen based on preliminary evidence that doses higher than those commonly prescribed could be more efficacious and provide better coverage for missed doses. Prior to the trial, we confirmed the tolerability of these doses alone and in combination in 2 randomized, placebo-controlled pilot studies.

Medical Management. Medical management was delivered by a licensed health care professional (14 physicians, 28 nurses, 1 physician assistant, 1 clinical pharmacist) over 9 sessions (weeks 0, 1, 2, 4, 6, 8, 10, 12, and 16) in which pills were dispensed. The initial visit averaged 45 minutes and began with a review of the alcohol dependence diagnosis and negative consequences of drinking. The professional recommended abstinence, provided education about the medications, and developed a medication adherence plan in collaboration with the patient. Attendance at support groups available in the community (eg, Alcoholics Anonymous) was encouraged. Subsequent sessions, averaging 20 minutes, included review of drinking, overall functioning, medication adherence, and adverse effects. Participants who resumed drinking were given advice and encouraged to attend support groups. Problems with medication adherence were addressed. Participants who discontinued medication because of intolerance continued in medical management sessions to support abstinence. For the CBI no pill group, access to health care professionals was available at weeks 4, 8, 12, and 16 to assess liver function and provide health care advice.

Combined Behavioral Intervention. The CBI was delivered by licensed behavioral health specialists (all with at least master’s degrees in psychology, social work, or counseling) in up to twenty 50-minute sessions. It integrated aspects of cognitive behavioral therapy, motivational interviewing, and support system involvement external to the study. Flexibility was permitted in the number of sessions and selection of modules to address each participant’s needs. A motivational interviewing style was used throughout.

Treatment Quality Assurance. All medical management practitioners and CBI counselors had professional degrees and at least 2 years of postdegree experience. Treatment professionals were trained by standard protocols and used intervention manuals. Before treating participants, treatment professionals submitted at least 2 tape-recorded cases and were certified by the training center. Sessions were audiotaped, with 8% (medical management) or 12% (CBI) monitored and corrective action taken to ensure adherence.

Statistical Methods

The primary goal of the COMBINE Study was to determine if improvement in treatment outcome could be achieved by combining pharmacotherapies and behavioral interventions. To evaluate this, 8 of the treatment combinations were chosen to form a 2 (acamprosate/placebo) × 2 (naltrexone/placebo) × 2 (CBI/no CBI) factorial design. This allowed estimation and testing of the effects of each of the interventions as monotherapies, as well as comparisons of the effects of each combination of 2 of the 3 therapies and of all 3 therapies combined. Thus, as described in detail previously, the primary hypotheses of the COMBINE Study were the testing of the conventional analysis of variance main effects for naltrexone, acamprosate, or CBI, as well as interaction effects.

The protocol prospectively specified 2 primary intent-to-treat efficacy analyses, based on the 8 groups that received pills. The coprimary end points were percent days abstinent and time to first heavy drinking day (≥5 standard drinks per day for men, ≥4 for women) during the 16-week treatment period. A standard drink was 0.5 oz of absolute alcohol, equivalent to 10 oz of beer, 4 oz of wine, or 1.0 oz of 100-proof liquor. Participants lost to follow-up (6%) were assumed to have resumed heavy drinking on the day after their last contact.

For each dependent variable, a 2 (acamprosate/placebo) × 2 (naltrexone/placebo) × 2 (CBI/no CBI) factorial model was fit. A mixed-effects general linear model was used for percent days abstinent. The 3 treatments (acamprosate, naltrexone, and CBI) were analyzed as fixed effects and time (month since randomization) as a repeated-measures effect. An analogous proportional hazards model was used to analyze the time to the first heavy drinking. The percentage of total individuals who relapsed (≥1 day of heavy drinking) by the end of treatment was derived from this analysis and presented for greater clinical clarity. Baseline percent days abstinent (within 30 days prior to the participant’s last drink) and research site were covariates for both the linear and proportional hazard models. A Bonferroni-corrected significance level of P = .025 (97.5% confidence interval...
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Results and Discussion

Pharmacotherapies and Behavioral Interventions for Alcohol Dependence

Val [CI] was set a priori to adjust for the 2 coprimary end points. The traditional factorial analysis of variance approach was adopted, evaluating interactions and main effects of the 3 treatments at this .025 level, without further adjustment for multiplicity.

Power for detecting a 10% main effect of each treatment was estimated to be greater than 0.90 for each coprimary end point. Estimated power for detecting an interaction effect of half the magnitude of the main effects was estimated to be lower but acceptable (eg, 0.40-0.50). The steering committee had extended discussion of the relative importance of providing definitive evaluations of the main effects of the treatments (eg, the efficacy of naltrexone, ignoring acamprosate and psychotherapy) vs evaluating interaction effects. The only way to have ample power for interactions would have been to use an incomplete factorial design that would have made untenable assumptions about main effects. Ultimately, it was decided that it was preferable to ensure sensitive, reliable assessments of the main effects, settling for modest power for interactions.

Preplanned interim analyses, reported to a data and safety monitoring board, were performed 18, 24, and 30 months after the first participant was randomized. A Lan-DeMets spending function approach was used to monitor the need for early trial termination.

Preplanned secondary analyses included evaluations of site x treatment interactions, alternative summary measures of drinking, outcome parameters other than drinking, and adjustment for various baseline prognostic factors. We also used a composite secondary outcome measure,31 in which a good clinical outcome was categorized as abstinence or moderate drinking without problems. Moderate drinking was defined as a maximum of 11 (women) or 14 (men) drinks per week, with no more than 2 days on which more than 3 drinks (women) or 4 drinks (men) were consumed. Problems were defined as endorsing 3 or more items on a standardized questionnaire22 assessing physical, social, and psychological consequences of drinking. Logistic models were used to evaluate the effect of treatment on clinical outcome.

A preplanned secondary analysis was conducted to evaluate the effect of taking pills and medical management. These analyses compared the CBI-only condition with patients receiving placebo plus medical management and with those receiving placebo plus medical management plus CBI. Similar to the primary analyses described above, these included mixed models for percent days abstinent, proportional hazard models for time to heavy drinking, and a logistic regression model for the composite clinical outcome.

A preplanned secondary analysis was also conducted to evaluate the persistence or emergence of between-group drinking differences over the posttreatment period (from the end of week 16 through up to 1 year afterwards). This analysis used the same variables and analytic strategy used for the analysis of the 16-week within-treatment period.

Secondary analyses and decomposition of interaction effects are presented here when they facilitate interpretation of the primary analyses. Data were organized, archived, and analyzed by the coordinating center.

The proportion of patients reporting adverse events was tabulated and compared using chi² or Fisher exact tests, as appropriate. SAS version 8.2 (SAS Institute Inc, Cary, NC) was used for all analyses.

RESULTS

Study Population

Randomization began in January 2001, and follow-up of the last participant ended in January 2004. A total of 1383 patients (428 women and 955 men) were enrolled and randomly assigned (Figure 1 and Table 1), slightly more than the target of 1375 specified in the protocol. Participants’ median age was 44 years, 71% had at least 12 years of education, and 42% were married. Ethnic minorities comprised 23% (321) of the sample. In the 30 days prior to randomization, 2.3% of patients were medically detoxified and 7.7% received in-patient treatment. The percentage of individuals abstinent for 4, 5 to 7, 8 to 14, and 15 to 21 days at randomization were 42%, 24%, 18%, and 15%, respectively (not significantly different across treatment groups).

Seventy-six pretreatment characteristics were compared across groups (saliency ones are summarized in Table 1). The only nominally significant (P <.05) between-group comparison was the number of DSM-IV alcohol dependence symptoms, which were 5.4 (SD, 1.3) for the collapsed medical management plus CBI groups and 5.6 (SD, 1.3) for the collapsed medical management without CBI groups. Thus, the groups were comparable on pretreatment characteristics.

Data Completeness

There were no statistically significant differences in research retention between treatment groups; although a number of people did not complete 1 or more aspects of treatment, 94% (group range, 92%-96%) provided complete within-treatment (weeks 1-16) drinking data. The average 1-year posttreatment drinking data completion rate was 82.3% (range, 80%-87%), with no significant difference between treatment groups.

Medication Adherence/Dose Reductions

Mean medication adherence, computed as the ratio of pills taken from returned blister pack counts to those prescribed throughout 16 weeks of treatment, was 85.8% (median, 96.4%). Mean adherence rates were similar for acamprosate (84.2%) and naltrexone (85.4%) and for those who received CBI (85.3%) or not (86.3%). Ongoing or recurrent dose reductions were 7.8% for placebo, 11.9% for acamprosate, 12.1% for naltrexone, and 20.9% for acamprosate plus naltrexone (P <.001). On average, 88 mg of naltrexone and 2537 mg of acamprosate were taken daily.

Adherence in Behavioral Interventions

The median CBI and medical management sessions completed were 10 and...
9, respectively. Therapists’ adherence ratings measured on six 7-point scales99 were high, with a median score of 6 for both medical management and CBI ratings (where a rating of 5 indicated acceptable protocol adherence). Alcoholics Anonymous attendance rates during treatment were similar across treatment groups, ranging from 17% to 35% (6-15 median meetings attended).

Biological Verification of Drinking

Level of %CDT, an abnormal serum transferrin protein altered by alcohol consumption, was used as a veracity check for self-reported drinking. Participants reporting complete abstinence over the study (n=212) had a 15% decrease in level of %CDT, whereas those reporting any drinking (n=694) had a 5% increase from baseline to week 16 (P<.001).

Table 1. Baseline Characteristics of Participants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Medical Management (No CBI)</th>
<th>CBI + Medical Management</th>
<th>CBI Only</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (n = 153)</td>
<td>Naltrexone (n = 152)</td>
<td>Acamprosate (n = 152)</td>
</tr>
<tr>
<td>Demographics, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>44.2 (9.15)</td>
<td>44.4 (9.13)</td>
<td>43.9 (10.97)</td>
</tr>
<tr>
<td>Men</td>
<td>103 (67.3)</td>
<td>105 (68.2)</td>
<td>105 (69.1)</td>
</tr>
<tr>
<td>Married</td>
<td>68 (44.4)</td>
<td>59 (38.3)</td>
<td>55 (36.2)</td>
</tr>
<tr>
<td>Employed</td>
<td>122 (78.9)</td>
<td>112 (72.7)</td>
<td>109 (71.7)</td>
</tr>
<tr>
<td>Education ≤high school</td>
<td>45 (29.4)</td>
<td>55 (35.7)</td>
<td>39 (25.7)</td>
</tr>
<tr>
<td>Race/ethnicity</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>120 (78.4)</td>
<td>108 (70.1)</td>
<td>122 (80.3)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>17 (11.1)</td>
<td>25 (16.2)</td>
<td>15 (9.9)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>81 (52.9)</td>
<td>83 (53.9)</td>
<td>74 (48.7)</td>
</tr>
</tbody>
</table>

Alcohol use severity indicators, mean (SD)†

| Percentage days absent | 24.3 (24.74) | 29.8 (24.70) | 24.6 (24.78) | 22.9 (24.70) | 24.3 (24.73) | 23.7 (24.78) | 25.3 (24.70) | 26.8 (24.68) | 23.5 (25.33) | .34 |
| Drinker Inventory of Consequences (maximum possible score, 135); OCDS, Obsessive Compulsive Drinking Scale (14 items; maximum possible score, 56).
| Eating guidelines | 0.7 (0.7) | 0.7 (0.7) | 0.7 (0.7) | 0.7 (0.7) | 0.7 (0.7) | 0.7 (0.7) | 0.7 (0.7) | 0.7 (0.7) | 0.7 (0.7) | .99 |
| Binge drinking | 20.1 (8.53) | 19.0 (8.56) | 19.6 (8.51) | 20.1 (8.52) | 20.1 (8.49) | 19.7 (8.47) | 19.5 (8.48) | 19.1 (8.52) | 19.6 (8.79) | .96 |
| DSM-IV symptoms‡ | 5.5 (1.28) | 5.5 (1.27) | 5.7 (1.34) | 5.7 (1.38) | 5.4 (1.25) | 5.4 (1.23) | 5.5 (1.32) | 5.5 (1.31) | 5.4 (1.41) | .38 |
| ADS score | 16.5 (7.15) | 17.5 (7.92) | 17.6 (7.38) | 16.8 (7.70) | 16.4 (7.31) | 16.3 (7.23) | 16.5 (7.40) | 16.0 (6.81) | 16.6 (6.97) | .59 |
| OCDS score | 24.5 (7.55) | 24.6 (7.57) | 26.3 (7.64) | 25.3 (7.66) | 25.1 (7.62) | 25.6 (7.59) | 26.2 (7.62) | 25.2 (7.52) | 18.9 (9.98) | .47 |
| DrInC score | 46.0 (20.16) | 48.1 (20.10) | 52.1 (20.10) | 47.5 (20.19) | 46.4 (20.11) | 47.5 (20.17) | 46.5 (20.15) | 48.1 (20.17) | 45.8 (20.29) | .24 |
| GGT, IU/L | 70.4 (79.80) | 68.9 (79.39) | 73.7 (154.90) | 66.2 (70.2) | 62.6 (67.86) | 68.5 (82.33) | 68.5 (79.94) | 85.9 (139.40) | 68.5 (96.05) | .72 |
| %CDT | 3.9 (2.59) | 3.5 (2.05) | 3.5 (2.64) | 3.4 (2.09) | 3.3 (1.59) | 3.1 (1.85) | 3.1 (1.63) | 3.6 (2.23) | .23 |
| %CDT >2.6, No. (%) | 73 (54) | 70 (51) | 70 (53) | 66 (51) | 68 (50) | 70 (53) | 62 (50) | 70 (51) | 75 (50) | .99 |

Abbreviations: ADS, Alcohol Dependence Scale (maximum possible score, 47); CBI, combined behavioral intervention; %CDT, percent carbohydrate-deficient transferrin; DrInC, Drinker Inventory of Consequences (maximum possible score, 135); DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; GGT, γ-glutamyltransferase; OCDS, Obsessive Compulsive Drinking Scale (14 items; maximum possible score, 56).

9 The 30 days prior to randomization was the baseline time frame used to compute percent days absent, drinks per drinking day, drinks per day, and heavy drinking days.
10 Heavy drinking days are defined as ≥4 drinks/d for women and ≥5 drinks/d for men.

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factors. A significant main effect of site was found in most analyses. No significant site × treatment interactions were found in any analysis. Therefore, as prespecified in the protocol, all analyses control for site as a baseline covariate.

Primary Outcomes. Table 3 and Table 4 present the estimated effects and associated P values for the protocol-specified main effects and interactions for percent days abstinent and time to first heavy drinking day. Figure 2 presents effect sizes and hazard ratios (HRs) for main effects and interaction effects. Table 5 provides the individual treatment group means.

For percent days abstinent, the 3-factor interaction (naltrexone × acamprosate × CBI) was not significant (P = .009) (Table 3). No other interactions were significant; nor were any of the main effects for acamprosate, naltrexone, or CBI. However, given the naltrexone × CBI interaction, the main-effect tests for naltrexone and CBI should be interpreted with caution. Examination of the least-squares means associated with this interaction (Table 3) shows that the participants receiving neither naltrexone nor CBI had the fewest abstinent days, whereas those participants receiving either naltrexone or CBI showed the most abstinence. Combined therapy with naltrexone plus CBI showed no incremental benefit over CBI or naltrexone alone. The effect size for the comparison of naltrexone to placebo in the absence of CBI was 0.22 (97.5% CI, 0.03-0.40) (Figure 2).

No significant main effects or interactions involving acamprosate, with or without CBI, were observed for time to the first heavy drinking day. However, there was a significant main effect of naltrexone (HR, 0.72; 97.5% CI, 0.53-0.98; P = .02) for time to first heavy drinking day (Table 4). Groups receiving naltrexone had, on average, a lower risk of heavy drinking than those receiving placebo. Although the naltrexone × CBI interaction was not significant for this end point (P = .15), the pattern of results is identical to that found for percent days abstinent (Table 4): in the context of medical management, those not receiving naltrexone or CBI fared worst, the group receiving naltrexone without CBI fared best, and the CBI plus placebo and CBI plus naltrexone groups

Table 2. Adverse Events During Treatment by Medication Group

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo (n = 309)</th>
<th>Acamprosate (n = 303)</th>
<th>Naltrexone (n = 309)</th>
<th>Acamprosate + Naltrexone (n = 305)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>65 (21)</td>
<td>72 (24)</td>
<td>101 (34)</td>
<td>125 (42)†</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Vomiting</td>
<td>26 (9)</td>
<td>27 (9)</td>
<td>45 (15)‡</td>
<td>52 (18)§</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>108 (35)</td>
<td>193 (65)†</td>
<td>92 (31)‡</td>
<td>165 (56)†</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>41 (13)</td>
<td>57 (19)</td>
<td>63 (21)</td>
<td>75 (25)†</td>
<td>.002</td>
</tr>
<tr>
<td>Somnolence</td>
<td>72 (24)</td>
<td>94 (31)§</td>
<td>112 (37)§</td>
<td>91 (31)†</td>
<td>.003</td>
</tr>
<tr>
<td>AST or ALT ≥ 5 times upper limit normal</td>
<td>0 (0)</td>
<td>1 (0)</td>
<td>6 (2)‡</td>
<td>5 (2)‡</td>
<td>.02</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol detoxification</td>
<td>3 (1)</td>
<td>11 (4)‡</td>
<td>6 (2)</td>
<td>11 (4)‡</td>
<td>.58</td>
</tr>
<tr>
<td>Other</td>
<td>5 (2)</td>
<td>7 (2)</td>
<td>4 (1)</td>
<td>6 (2)</td>
<td>.80</td>
</tr>
<tr>
<td>Withdrawals due to adverse events</td>
<td>4 (1)</td>
<td>9 (3)</td>
<td>12 (4)</td>
<td>13 (4)‡</td>
<td>.09</td>
</tr>
</tbody>
</table>

Table 3. Adjusted Mean Percent Days Abstinent Through End of Treatment

<table>
<thead>
<tr>
<th>Mean (SD)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>Intervention</td>
</tr>
<tr>
<td>Placebo (n = 616)</td>
<td>Acamprosate (n = 605)</td>
</tr>
<tr>
<td>Main Effects</td>
<td></td>
</tr>
<tr>
<td>Acamprosate</td>
<td>77.6 (25.32)</td>
</tr>
<tr>
<td>Placebo (n = 610)</td>
<td>Naltrexone (n = 611)</td>
</tr>
<tr>
<td>Naltrexone</td>
<td>77.2 (25.42)</td>
</tr>
<tr>
<td>No CBI (n = 609)</td>
<td>CBI (n = 614)</td>
</tr>
<tr>
<td>CBI</td>
<td>77.8 (25.36)</td>
</tr>
</tbody>
</table>

| Interactions | |
| Placebo (n = 307) | Acamprosate (n = 303) |
| Acamprosate × naltrexone | 77.0 (25.82) | 78.2 (25.31) | .74 |
| Placebo (n = 303) | Naltrexone (n = 302) |
| Acamprosate (n = 303) | 77.3 (25.37) | 79.5 (25.37) | .74 |

| No CBI | CBI |
| Acamprosate × CBI | 77.3 (25.41) | 77.9 (24.90) | 84 |
| Placebo (n = 303) | Acamprosate (n = 305) |
| Placebo (n = 309) | Naltrexone (n = 303) |
| Acamprosate (n = 303) | 78.4 (25.84) | 78.4 (25.50) | .84 |

| No CBI | CBI |
| Naltrexone × CBI | 75.1 (25.46) | 80.6 (25.37) | .009 |

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

*Overall test for difference in proportions between treatments used χ² test for cell counts ≥5 and Fisher exact test for evaluation of smaller cell frequencies.

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were intermediate. Only the pairwise comparison of naltrexone vs placebo in the no-CBI (ie, medical management only) condition reached statistical significance; the other 2 comparisons showed trends in a consistent direction (Figure 2 and Figure 3).

Secondary Outcomes. Analyses of alternative summary measures of drinking, including drinks per drinking day (P=.03), drinks per day (P=.03), and heavy drinking days per month (P=.006), were consistent with those for the coprimary end points, all showing a significant naltrexone × CBI interaction.

Abstinence has been the primary end point for most acamprosate studies. Cumulative proportion of abstinence days is analogous to percent days abstinent in our study. We also examined time to first drink as a secondary outcome. None of the main effects or interactions were statistically significant, but the overall pattern of results is consistent with that for primary end points.

The Obsessive Compulsive Drinking Scales showed a main effect (P=.01) in which naltrexone was associated with lower craving than was
placebo (9.7 [SD, 7.60] vs 10.9 [SD, 7.64], respectively; P = .01). This effect remained significant (P = .02) if the obsessive factor score, not including the drinking items, was analyzed separately. A trend for a main effect favoring naltrexone (P = .08) was seen on a measure of alcohol-related consequences.52 Differential treatment effects were not seen on levels of γ-glutamyltransferase or %CDT.

Clinical Significance. Analysis of the composite outcome measure at end of treatment (Figure 4 and Table 5) revealed a significant interaction between naltrexone and CBI (P = .02), in which naltrexone, CBI, or both enhanced positive outcomes in the presence of medical management. The percentages of good clinical outcomes were 58% for the placebo/medical management group, 74% for the naltrexone/medical management group, 71% for the placebo/CBI plus medical management group, and 74% for the naltrexone/CBI plus medical management group. The numbers needed to treat (1/absolute risk reduction, which is the rate of good composite outcome for each group minus that for the placebo plus medical management group) to achieve these good composite outcomes are 7 for CBI, 6 for naltrexone, and 7 for naltrexone plus CBI. There were no other significant main or interactive effects.

Sex Effects. Overall, men had a slightly better outcome for percent days abstinent (men, 78.0 [SD, 29.12] vs women, 75.4 [SD, 19.44]; P = .04); however, sex did not significantly affect response to any of the treatments. It should be noted, however, that statistical power to detect small to moderate sex × treatment effects in this study was limited.

Within-Treatment Evaluation of CBI Therapy Without Pills (Placebo Effect) To evaluate the effect of taking pills and medical management on CBI, we contrasted the drinking outcomes (percent days abstinent, relapse rates, and clinical outcome) (Table 5) between those taking placebo who only received medical management (n = 153), those taking placebo who received medical management and CBI (n = 156), and those taking no pills who received only CBI (n = 157).

Percent Days Abstinent. During the 16 weeks of treatment, there was an overall difference (P < .001) in percent days abstinent between those receiving placebo pills and medical management alone (73.8), placebo pills and medical management plus CBI (79.8), and CBI alone (no pills or medical management) (66.6). Pairwise post hoc tests, corrected for multiple comparisons, showed a significant difference between those receiving pills and medical management compared with those...
receiving pills and medical management plus CBI (P = .04) and with those receiving CBI alone (P = .03). There was a larger difference between those receiving pills and medical management plus CBI and those receiving CBI alone (P < .001).

Relapse to Heavy Drinking. There was more relapse to heavy drinking in those receiving CBI alone (no pills or medical management) (79.0%) compared with those receiving pills and medical management plus CBI (71.2%) (HR, 0.77; 97.5% CI, 0.60-1.00; P = .05). The relapse rate to heavy drinking for the placebo pill and medical management group (75.2%) was intermediary to the other 2 groups and did not differ significantly from them.

Global Clinical Outcome. The percentage of patients receiving CBI only who had a good global clinical outcome (60.6%) was intermediate between those receiving placebo and medical management (58.2%) and those receiving placebo medical management and CBI (71.3%). Overall, the differences among these 3 groups were not significant (P = .07).

Posttreatment Follow-up Outcomes

Initial analyses were performed to evaluate potential confounding variables during the 1-year posttreatment follow-up period. Overall, frequency of hospitalization (11%), emergency department treatment for alcohol problems (6%), use of medication for drinking (11%) or emotional problems (17%), and detoxification (6%) were not significantly different between the treatment groups (TABLE 6).

Percent Days Abstinent. Overall, percent days abstinent declined across groups during the year after treatment ended.

While the direction of the differences observed during treatment remained in the posttreatment period (TABLE 7), the naltrexone × CBI interaction was no longer significant. Those treated with placebo and medical management had lower mean percent days abstinent (61.4%) compared with those treated with naltrexone and medical management (66.2%) and with those treated with CBI with naltrexone (67.3) or without (66.6). Overall, there was a trend (P = .08) for CBI-treated individuals to have higher percent days abstinent than those treated with medical management, irrespective of medication group. The overall percent days abstinent in those who received CBI without pills (60.9%), those who received placebo and medical management (59.4), and those who received placebo plus medical management and CBI (67.5) were no longer significantly different (P = .08).

Relapse to Heavy Drinking. Overall, more individuals had at least 1 heavy drinking day during the posttreatment

---

**Figure 4.** Odds Ratios for Good Composite Clinical Outcome at End of Treatment Compared With Placebo Naltrexone/No Combined Behavioral Intervention (CBI)

Logistic regression model of good clinical outcome (see "Methods" for definition) at the end of the last 8 weeks of treatment was significant for naltrexone\(\times\)CBI interaction, \(P = .02\). CI indicates confidence interval.

**Table 6. Description of Medical Interventions During 1-Year Posttreatment in Participants**

<table>
<thead>
<tr>
<th>Behavioral Intervention</th>
<th>Medical Management (No CBI)</th>
<th>CBI + Medical Management</th>
<th>CBI Only Medical Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>Placebo (n = 153) Naltrexone (n = 154) Acamprosate (n = 152) Naltrexone + Acamprosate (n = 148)</td>
<td>Placebo (n = 156) Naltrexone (n = 155) Acamprosate (n = 151) Naltrexone + Acamprosate (n = 157)</td>
<td>Placebo (n = 157) Naltrexone (n = 157) Acamprosate (n = 157) CBI Only No Pills (n = 157)</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>26 (17.0) 28 (18.2) 26 (17.1) 25 (16.9) 22 (14.1) 25 (16.1) 21 (13.9) 32 (20.4) 34 (21.7)</td>
<td>68</td>
<td></td>
</tr>
</tbody>
</table>

Individuals with various posttreatment medical interventions:

- Hospital or other facility: 20 (13.1) 16 (10.4) 19 (12.5) 19 (12.8) 16 (10.3) 12 (7.7) 12 (7.9) 13 (8.3) 20 (12.7) .60
- ED for alcohol treatment: 9 (5.9) 11 (7.1) 11 (7.2) 11 (7.4) 10 (6.4) 9 (5.8) 4 (2.6) 7 (4.5) 11 (7.0) .73
- Medication for drinking: 20 (13.1) 19 (12.3) 21 (13.8) 10 (6.8) 19 (12.2) 20 (12.9) 15 (9.9) 13 (8.3) 9 (5.7) .17
- Psychiatric medication: 29 (19.0) 24 (15.6) 23 (15.1) 18 (12.2) 24 (15.4) 27 (17.4) 22 (14.6) 27 (17.2) 37 (23.6) .32
- Detoxification medication: 14 (9.2) 7 (4.5) 9 (5.9) 9 (6.1) 8 (5.1) 3 (1.9) 6 (4.0) 10 (6.4) 10 (6.4) .32

Abbreviations: CBI, combined behavioral intervention; ED, emergency department.

*Overall test for differences in proportions used \(\chi^2\) test to estimate \(P\) values. Lost to follow-up means drinking data not available at the final assessment time 1 year after treatment. Data shown are outcome variables but only descriptions of self-reported events occurring during the posttreatment follow-up period.
period (Table 8) than during treatment. The direction of the effects observed during treatment persisted, with only those receiving naltrexone showing nominally less risk (HR, 0.77; 97.5% CI, 0.58-1.02; \( P = .04 \)) of returning to at least 1 heavy drinking day over time. No other medication or medication by behavioral therapy interaction was significant. The CBI-no pills group had a nonsignificantly greater rate of at least 1 heavy drinking day (86.6%) than the placebo and medical management group (84.3%) or the placebo and medical management plus CBI group (80.8%).

Global Clinical Outcome. There was no significant overall group difference in global clinical outcome as assessed over the last 16 weeks of the 1-year follow-up period. It should be noted that the group initially treated with placebo and medical management had the least number of participants with a good clinical response at the end of the 1-year posttreatment follow-up period (Table 9), consistent with that observed at the end of the treatment period. The CBI-no pills group no longer differed significantly from the CBI-placebo or the medical management-placebo groups (Table 9).

**COMMENT**

As in prior multisite trials of treatment for alcoholism, all treatment groups experienced a large increase in percent days abstinent, from 25 prestudy to 73 during treatment. Across several drinking measures, patients receiving medical management showed better outcomes when also receiving either CBI or naltrexone: in the absence of CBI, naltrexone helped; without naltrexone, CBI helped. The combination of CBI plus naltrexone did not further improve outcomes. With regard to naltrexone, the reduction in risk for a first heavy drinking day was 0.28, consistent with meta-analyses of other naltrexone trials that used 50 mg/d and included specialist care. However, our findings stand in contrast to the negative results of the multisite Veterans Affairs Naltrexone Cooperative Study. Potential reasons for discrepancy between our results and those of that study, and possibly those of others, relate to differences in participant characteristics, the use of 12-step facilitation therapy, the high placebo response rate, lower follow-up rate, and smaller sample size in that trial. Nevertheless, our data suggest that naltrexone can be effective within the context of medical management without specialist behavioral treatment.

The lack of acamprosate efficacy was surprising, given the positive results of many previous trials. Our study used a higher dosage (3 g/d) than that used in most trials (approximately 2 g/d), although exploratory analyses of a US multisite study of acamprosate found efficacy for the 3-g/d dosage, whereas the 2-g/d dosage was not of significant benefit in the intention-to-treat analysis. Neither adverse events nor medication adherence appeared to be especially problematic with the 3-g/d dosage used in our study. One salient difference is that our trial required only 4 days of abstinence, achieved primarily on an outpatient basis, whereas most positive studies of acamprosate had a longer pretreatment abstinence period established during inpatient treatment. Also, prior acamprosate trials used less frequent assessment, nonstandardized counseling, and patients recruited from clinical (primarily inpatient) settings.

Consistent with our pilot studies, the combined use of naltrexone and acamprosate appeared to be safe and well tolerated. However, contrary to our study hypothesis and trends observed in a single-site study, our current data do not support the combined use of these 2 medications.

Previous trials reported an advantage of pairing naltrexone with specialist-delivered behavioral therapy. In the COMBINE Study, however, comparable outcomes were produced by CBI alone, naltrexone alone, and the combination of CBI and naltrexone, if pro-

---

Table 7. Adjusted Mean Percent Days Abstinent Through the End of Follow-up

<table>
<thead>
<tr>
<th>Control</th>
<th>Intervention</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>P Value</td>
</tr>
<tr>
<td><strong>Placebo</strong></td>
<td><strong>Acamprosate</strong></td>
<td><strong>Placebo</strong></td>
</tr>
<tr>
<td>(n = 286)</td>
<td>(n = 283)</td>
<td>(n = 287)</td>
</tr>
<tr>
<td>Placebo</td>
<td>Acamprosate</td>
<td>Placebo</td>
</tr>
<tr>
<td>(n = 286)</td>
<td>(n = 283)</td>
<td>(n = 287)</td>
</tr>
<tr>
<td>Placebo</td>
<td>Acamprosate</td>
<td>Placebo</td>
</tr>
<tr>
<td>(n = 286)</td>
<td>(n = 283)</td>
<td>(n = 287)</td>
</tr>
<tr>
<td>Placebo</td>
<td>Acamprosate</td>
<td>Placebo</td>
</tr>
<tr>
<td>(n = 286)</td>
<td>(n = 283)</td>
<td>(n = 287)</td>
</tr>
<tr>
<td>Placebo</td>
<td>Acamprosate</td>
<td>Placebo</td>
</tr>
<tr>
<td>(n = 286)</td>
<td>(n = 283)</td>
<td>(n = 287)</td>
</tr>
</tbody>
</table>

Abbreviation: CBI, combined behavioral intervention.

*Adjusted least-squares means (SDs) from a mixed model that adjusts for clinical center and baseline percent days abstinent, fitting all main effects and 2- and 3-factor interactions.

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vided in the context of medical management. The lack of additive effect of CBI and naltrexone in this study might be attributable to methodological differences between studies, including the higher naltrexone dosage in this study. Also, all pill-taking participants received 9 sessions of medical management in addition to medication and CBI, perhaps making it difficult to show an added advantage for the combination of CBI plus naltrexone over either alone.

Moreover, while CBI in this study incorporated components of cognitive-behavioral therapy, it differs in many ways\(^{41}\) from standard cognitive-behavioral therapy, including a greater emphasis on Alcoholics Anonymous attendance. Our results, however, are consistent with those of O’Malley et al.\(^{59}\) who found that naltrexone did not contribute to the maintenance of improvement in patients who initially responded to naltrexone and CBI but did for those patients who received a primary care model of counseling.

Our data support previous results\(^{59,60}\) suggesting that naltrexone can be a viable medical management option for treating alcohol-dependent individuals. Although our medical management intervention\(^{39,40}\) is more intensive than that provided to alcohol-dependent patients in most health care settings, it is not too dissimilar to other common general medicine patient care activities, such as initiating insulin therapy in a patient with diabetes mellitus, initial management of human immunodeficiency virus medications, and intensive management of congestive heart failure. For individuals who prefer counseling rather than medication, CBI could be provided by a specialist counselor along with coordinated medical care.\(^{61}\)

In this study, the numbers needed to treat to achieve a good clinical outcome in medical management with either naltrexone or CBI were similar.

### Table 8. Participants With ≥1 Heavy Drinking Day Over 1 Year Posttreatment

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Intervention</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Main Effects</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>Placebo (n = 618)</td>
<td>Acamprosate (n = 608)</td>
<td></td>
</tr>
<tr>
<td>Acamprosate</td>
<td>498 (80.6)</td>
<td>485 (79.8)</td>
<td>.40</td>
</tr>
<tr>
<td>Placebo</td>
<td>Placebo (n = 612)</td>
<td>Naltrexone (n = 614)</td>
<td></td>
</tr>
<tr>
<td>Naltrexone</td>
<td>495 (80.9)</td>
<td>487 (79.5)</td>
<td>.04</td>
</tr>
<tr>
<td>No CBI</td>
<td>No CBI (n = 607)</td>
<td>CBI (n = 619)</td>
<td></td>
</tr>
<tr>
<td>CBI</td>
<td>495 (81.5)</td>
<td>488 (78.8)</td>
<td>.13</td>
</tr>
</tbody>
</table>

### Table 9. One-Year Posttreatment Drinking Outcomes

<table>
<thead>
<tr>
<th>Drinking Outcomes(^a)</th>
<th>Medical Management (No CBI)</th>
<th>CBI + Medical Management</th>
<th>CBI Only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent days absent, mean (SD)(^b)</td>
<td>Placebo (n = 1383)</td>
<td>59.4 (32.4)</td>
<td>68.1 (31.49)</td>
</tr>
<tr>
<td>Return to heavy drinking, No. of events (%)(^c)</td>
<td>Placebo (n = 153)</td>
<td>129 (84.3)</td>
<td>121 (78.6)</td>
</tr>
<tr>
<td>Good clinical outcome, No. of events (%)(^d)</td>
<td>Placebo (n = 153)</td>
<td>1033</td>
<td>43 (37.7)</td>
</tr>
</tbody>
</table>

**Abbreviation:** CBI, combined behavioral intervention.

\(a\) Numbers (percentages) of participants with a heavy drinking day at any time during the 1-y posttreatment period are given for clinical interpretation, but the statistical test is a proportional hazard model of time to the first day of heavy drinking over the 52-week posttreatment follow-up period, adjusting for clinical center and baseline percent days abstinent, fitting all main effects and 2- and 3-factor interactions.

\(b\) Percent days absent is computed monthly for the treatment period. At least 5 days of data per month were required to compute percent days absent; otherwise, it was considered missing.

\(c\) Heavy drinking day is defined as ≥4 drinks/d for women and ≥5 drinks/d for men.

\(d\) See “Methods” section for definition. The good clinical outcome at end of follow-up is derived from the assessment period covering the last 16 weeks of the study.
University of Miami School of Medicine, Miami, Fla (Drs Mason and Williams); National Eye Institute, National Institute of Alcohol Abuse and Alcoholism, Bethesda, Md (Dr Mattson); Center on Alcoholism, Substance Abuse and Addiction, University of New Mexico, Albuquerque (Dr Miller); Treatment and Research Center, University of Pennsylvania, Philadelphia (Dr Pettinati); and Harvard University/McLean Hospital, Belmont, Mass (Dr Weiss). Dr Gastfriend is now affiliated with Alkermes Inc, Cambridge, Mass; Dr Johnson is now with University of Virginia Health System, Charlottesville, Va; Dr Mason is now with The Scripps Research Institute, La Jolla, Calif; and Dr Zweben is now with Columbia University School of Social Work, New York, NY.

Author Contributions: Dr Hosking had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Hosking, Johnson, LoCastro, Longabaugh, Mason, Miller, Pettinati, Randall, Swift, Weiss, Zweben.

Critical revision of the manuscript for important intellectual content: Antón, O’Malley, Ciraulo, Cisler, Couper, Donovan, Gastfriend, Hosking, Johnson, LoCastro, Longabaugh, Mason, Mattson, Miller, Pettinati, Randall, Swift, Weiss, Zweben. Drafting of the manuscript: Antón, O’Malley, Donovan, Hosking, Miller, Weiss, Zweben. Statistical analysis: Couper, Hosking.


Administrative, technical, or material support: Antón, O’Malley, Ciraulo, Cisler, Couper, Donovan, Gastfriend, Hosking, Johnson, LoCastro, Longabaugh, Mason, Mattson, Miller, Pettinati, Randall, Swift, Weiss, Williams, Zweben.


Financial Disclosures: Dr Anton has reported receiving consultation fees and honoraria from Bristol-Myers Squibb and Hythium; consultation fees, and grants from Cephalon; and consultation fees from Ortho-McNeil, Pfizer, and Sanofi-Aventis. Dr O’Malley has reported receiving research support (grant funding or supplies) from Alkermes, Bristol-Myers Squibb, DuPont, Forest Laboratories, GlaxoSmithKline, Lippa Pharmaceuticals, Mallinckrodt, Ortho-McNeil, Pfizer, and Sanofi-Aventis; serving as a consultant for Alkermes, Forest Laboratories, GlaxoSmithKline, Johnson & Johnson/Ortho McNeil; consultation fees and grant funding from Pfizer; and consultation fees from AstraZeneca, Axix Shield, Cephalon, Drug Abuse Sciences, and Sanofi-Aventis. Dr Miller has reported receiving research support (grant funding or supplies) from Alkermes, Bristol-Myers Squibb, Ortho-McNeil, and Pfizer; receiving travel reimbursement from Alkermes; and reporting consultation fees from AstraZeneca, Axix Shield, Cephalon, Drug Abuse Sciences, and Sanofi-Aventis; serving as a consultant for Alkermes, Forest Laboratories, GlaxoSmithKline, Johnson & Johnson, Ortho-McNeil, and Pfizer; and receiving travel reimbursement from Alkermes.

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PHARMACOTHERAPIES AND BEHAVIORAL INTERVENTIONS FOR ALCOHOL DEPENDENCE

GlaxoSmithKline, and Johnson & Johnson/Ortho-McNeil. Dr. Hasan has received consulting fees and honoraria from Forest Laboratories and Lipha Pharmaceuticals; consulting fees and research support from Alkermes; and research support from Drug Abuse Sciences, Eli Lilly, Lipha-Merk-KgaA, Ortho-McNeil, and Pfizer; serving as a consultant for Alkermes, AstraZeneca, Alexia, Lipha Pharmaceuticals, Ortho-McNeil, and Pfizer; and may in the future receive grant support from Forest Laboratories. No other disclosures were reported.

Role of the Sponsors: This study was supported by National Institute on Alcohol Abuse and Alcoholism (NIAAA) Cooperative Agreements U10AA117195, 11716, 11721, 11727, 11756, 11768, 11773, 11776, 11777, 11778, 11787, 11789, 11796, 11797, 11849, 11864, 11873, 11899, and 11934, and National Heart, Lung, and Blood Institute scientists award K05AA014715, K05AA00133, K02DA00326, and K23DA00329. The acamprosate naltrexone, and their matching placebos used in this study were donated by Lipha Pharmaceuticals.

Acknowledgments: We thank Mark Willenbring, MD, NIAAA, and Patrick G. O'Connor, MD, Yale School of Medicine, for their thoughtful comments in the preparation of the article. We recognize the contribution of the many investigators and staff (especially Marston Youngblood, MA, MPH) whose efforts were necessary to plan and execute this project (a list of these individuals is available at http://www.cccc.unc.edu/combine).

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PHARMA Cand Behavioral Interventions for Alcohol Dependence


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(Reprinted) JAMA. May 3, 2006—Vol 295, No. 17

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