Combined Pharmacotherapies and Behavioral Interventions for Alcohol Dependence
The COMBINE Study: A Randomized Controlled Trial

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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 × 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.

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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. 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. 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) criteria, using the Structured Clinical Interview for DSM-IV; (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 baseline and during the 16-week treatment period 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 consumption and craving.

Similar to those represented in general population data, do not receive specialty care (National Institute on Alcohol Abuse and Alcoholism [NIAAA], unpublished data).

Primary care physicians can play a significant role in addressing alcohol use disorders. 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 treatments and at least 2 medications approved by the US Food and Drug Administration, naltrexone and acamprosate, 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 unclear whether combining naltrexone (an opiate receptor antagonist) with acamprosate (a putative glutamate modulator) 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. 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]).

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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 healthcare 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**
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.25,30 Prior to the trial, we confirmed the tolerability of these doses alone and in combination in 2 randomized, placebo-controlled pilot studies.37,38

Medical Management. Medical management39,40 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,41 12-step facilitation,42 motivational interviewing,43 and support system involvement external to the study.44,45 Flexibility was permitted in the number of sessions and selection of modules to address each participant's needs. A motivational interviewing46 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.39,41 Before treating participants, treatment professionals submitted at least 2 tape-recorded cases and were certified by the training center.46 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,12,22 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.22 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.49 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 day. 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 \( P = 0.025 \) (97.5% confidence inter-
come measure,51 in which a good clini-
also used a composite secondary out-
various baseline prognostic factors. We
other than drinking, and adjustment for
interactions, alternative summary mea-
tation approach was used to monitor the
ported to a data and safety monitoring
assessments of the main effects, settling for
able to ensure sensitive, reliable as-
assumptions about main effects. Ulti-
that would have made untestable
samplespower for interactions would have
ample power for interactions would have
ample factorial design
would have made untestable assumptions about main effects. Uli-
ally, it was decided that it was pref-
erable to ensure sensitive, reliable as-
ssessments of the main effects, settling for
modest power for interactions.
Preplanned interim analyses, re-
ported to a data and safety monitoring
board, were performed 18, 24, and 30
months after the first participant was ran-
ized.22 A Lan-DeMets spending func-
tion approach was used to monitor the
need for early trial termination.
Preplanned secondary analyses in-
cluded evaluations of site × treatment in-
teractions, alternative summary mea-
ures of drinking, outcome parameters
other than drinking, and adjustment for
various baseline prognostic factors. We
also used a composite secondary out-
come measure,31 in which a good clini-
cal outcome was categorized as absti-
ence or moderate drinking without
problems. Moderate drinking was de-
ined as a maximum of 11 (women) or
14 (men) drinks per week, with no more
2 days on which more than 3 drinks
(women) or 4 drinks (men) were con-
sumed. Problems were defined as en-
dorsing 3 or more items on a standard-
ized questionnaire32 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 tak-
ing pills and medical management. These
analyses compared the CBI-
only condition with patients receiving
placebo plus medical management and
with those receiving placebo plus medi-
cal management plus CBI. Similar to the
primary analyses described above, these
included mixed models for percent days
abstinent, proportional hazard mod-
els for time to heavy drinking, and a lo-
gistic regression model for the com-
posite clinical outcome.
A preplanned secondary analysis was
also conducted to evaluate the persis-
tence or emergence of between-group
drinking differences over the posttreat-
ment 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 decomposi-
tion of interaction effects are pre-
ented here when they facilitate inter-
pretation of the primary analyses. Data
were organized, archived, and ana-
lyzed by the coordinating center.
The proportion of patients report-
ing adverse events was tabulated and
compared using χ2 or Fisher exact tests,
as appropriate. SAS version 8.2 (SAS In-
stitute 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. Eth-
nic minorities comprised 23% (321) of
the sample. In the 30 days prior to ran-
donization, 2.3% of patients were medi-
cally detoxified and 7.7% received in-
patient treatment. The percentage of
individuals abstinent for 4, 5 to 7, 8 to
14, or 15 to 21 days at randomization
were 42%, 24%, 18%, and 15%, re-
spectively (not significantly different across
treatment groups).
Seventy-six pretreatment character-
istics were compared across groups (sa-
lient ones are summarized in Table 1).
The only nominally significant (P<.05)
between-group comparison was the
number of DSM-IV alcohol depen-
dence symptoms, which were 5.4 (SD,
1.3) for the collapsed medical manage-
ment plus CBI groups and 5.6 (SD, 1.3)
for the collapsed medical manage-
ment without CBI groups. Thus, the
groups were comparable on pretreat-
ment 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 as-
pects of treatment, 94% (group range,
92%-96%) provided complete within-
treatment (weeks 1-16) drinking data.
The average 1-year posttreatment drink-
ing data completion rate was 82.3%
(range, 80%-87%), with no significant
difference between treatment groups.

Medication Adherence/
Dose Reductions
Mean medication adherence, com-
cuted 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 re-
current dose reductions were 7.8% for
placebo, 11.9% for acamprosate, 12.1%
for naltrexone, and 20.9% for acam-
prosate 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 manage-
ment sessions completed were 10 and
9, respectively. Therapists’ adherence ratings measured on six 7-point scales 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 treatment groups, ranging from 17% to 35% (6-15 median meetings attended).

### Adverse Events

Of 70 serious adverse events occurring during treatment, 2 were possibly related to study medication (1 naltrexone, 1 acamprosate). The most common serious adverse event was hospitalization for detoxification (n = 38). The rates of serious adverse events were similar across groups, as were adverse events leading to treatment dropout (Table 2). However, there were significant differences in the percentages reporting nausea (P < .001), vomiting (P < .001), diarrhea (P < .001), decreased appetite (P < .002), and somnolence (P < .003) (Table 2). Twelve participants, primarily in the naltrexone groups, had treatment-emergent levels of liver enzymes (aspartate aminotransferase or alanine aminotransferase) greater than 5 times the upper limit of normal (P = .02). These results followed the discontinuation of medication, except for 2 cases (1 participant did not return for retesting; the other continued heavy drinking).

### Within-Treatment Drinking Outcomes for Pill-Taking Groups

**Time Effects.** Overall, percent days abstinent from baseline to end of study tripled from 25.2 to 73.1 (P < .001), and drinks per drinking day declined by 44%, from 12.6 to 7.1 (P < .03), with the net effect that alcohol consumption decreased by 80%, from 66 to 13 drinks per week.

**Site Effects.** It was anticipated, a priori, that there would be differences in outcome among sites, based on differences in patient populations, effectiveness of therapists, and other local

### 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 No Pills (Pills)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics, No. (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>44.2 (9.15)</td>
<td>44.4 (9.93)</td>
<td>43.2 (9.74)</td>
<td>.63</td>
</tr>
<tr>
<td>Men</td>
<td>103 (67.3)</td>
<td>105 (68.2)</td>
<td>107 (68.4)</td>
<td>.99</td>
</tr>
<tr>
<td>Married</td>
<td>68 (44.4)</td>
<td>59 (38.3)</td>
<td>70 (50.0)</td>
<td>.99</td>
</tr>
<tr>
<td>Employed</td>
<td>122 (78.7)</td>
<td>112 (72.7)</td>
<td>119 (78.8)</td>
<td>.57</td>
</tr>
<tr>
<td>Education (&lt; high school)</td>
<td>49 (29.4)</td>
<td>55 (35.7)</td>
<td>41 (26.5)</td>
<td>.69</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>120 (78.4)</td>
<td>108 (70.1)</td>
<td>113 (70.9)</td>
<td>.43</td>
</tr>
<tr>
<td>Black</td>
<td>10 (6.5)</td>
<td>11 (7.4)</td>
<td>9 (5.8)</td>
<td>.55</td>
</tr>
<tr>
<td>Hispanic</td>
<td>17 (11.1)</td>
<td>25 (16.2)</td>
<td>16 (10.6)</td>
<td>.43</td>
</tr>
<tr>
<td>Current smoker</td>
<td>81 (52.9)</td>
<td>83 (53.7)</td>
<td>84 (54.2)</td>
<td>.54</td>
</tr>
<tr>
<td><strong>Alcohol use severity indicators, mean (SD)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percent days abstinent</td>
<td>24.3 (24.74)</td>
<td>29.8 (24.70)</td>
<td>23.7 (24.78)</td>
<td>.34</td>
</tr>
<tr>
<td>Drinks per drinking day</td>
<td>12.6 (7.67)</td>
<td>12.7 (7.69)</td>
<td>12.4 (7.72)</td>
<td>.95</td>
</tr>
<tr>
<td>Overall drinks per day</td>
<td>9.6 (6.43)</td>
<td>8.9 (6.45)</td>
<td>9.1 (6.41)</td>
<td>.97</td>
</tr>
<tr>
<td>Heavy drinking days†</td>
<td>20.1 (8.53)</td>
<td>19.0 (8.56)</td>
<td>19.6 (8.51)</td>
<td>.97</td>
</tr>
<tr>
<td>DSM-IV symptoms‡</td>
<td>5.5 (1.28)</td>
<td>5.5 (1.27)</td>
<td>5.5 (1.23)</td>
<td>.88</td>
</tr>
<tr>
<td>ADS score</td>
<td>16.5 (7.15)</td>
<td>17.5 (7.92)</td>
<td>16.4 (7.31)</td>
<td>.59</td>
</tr>
<tr>
<td>OCDS score</td>
<td>24.5 (7.55)</td>
<td>24.6 (7.57)</td>
<td>25.1 (7.62)</td>
<td>.47</td>
</tr>
<tr>
<td>DrInC score</td>
<td>46.5 (20.16)</td>
<td>48.1 (20.13)</td>
<td>46.5 (20.15)</td>
<td>.24</td>
</tr>
<tr>
<td>GGT, IU/L</td>
<td>70.4 (79.80)</td>
<td>68.5 (93.75)</td>
<td>68.5 (82.33)</td>
<td>.72</td>
</tr>
<tr>
<td>%CDT</td>
<td>3.9 (2.59)</td>
<td>3.5 (2.05)</td>
<td>3.5 (2.06)</td>
<td>.23</td>
</tr>
<tr>
<td>%CDT &gt; 2.6, No. (%)</td>
<td>73 (54)</td>
<td>70 (53)</td>
<td>66 (51)</td>
<td>.99</td>
</tr>
</tbody>
</table>

**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, 130); 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). 

*The 30 days prior to randomization was the baseline time frame used to compute percent days abstinent, drinks per drinking day, drinks per day, and heavy drinking days.

†Heavy drinking days are defined as ≥4 drinks/d for women and ≥5 drinks/d for men.

‡The SCD DSM-IV Module E was used to assess symptoms.
factors. A significant main effect of site was found in most analyses. No significant site × treatment interactions were found in any analysis. Therefore, as pre-specified 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>Alcohol detoxification</td>
<td>3 (1)</td>
<td>11 (4)‡</td>
<td>6 (2)</td>
<td>11 (4)‡</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>

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.
†P < .01 or placebo vs active drug comparison.
‡P < .05 for placebo vs active drug comparison.
§P < .01 for placebo vs active drug comparison.

†One fatal serious adverse event was reported during the 16-week treatment phase. This was classified by investigators as not related to study medication.

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

<table>
<thead>
<tr>
<th>Event</th>
<th>Control (n = 616)</th>
<th>Intervention (n = 605)</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>77.6 (25.32)</td>
<td>78.4 (25.31)</td>
<td>.61</td>
</tr>
<tr>
<td>Acamprosate</td>
<td>77.2 (25.42)</td>
<td>78.8 (25.46)</td>
<td>.25</td>
</tr>
<tr>
<td>Naltrexone</td>
<td>77.2 (25.36)</td>
<td>78.2 (25.52)</td>
<td>.82</td>
</tr>
<tr>
<td>No CBI</td>
<td>77.8 (25.36)</td>
<td>78.2 (25.52)</td>
<td>.82</td>
</tr>
<tr>
<td>CBI</td>
<td>77.7 (25.36)</td>
<td>78.2 (25.52)</td>
<td>.82</td>
</tr>
<tr>
<td><strong>Interactions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acamprosate × naltrexone</td>
<td>77.0 (25.82)</td>
<td>78.2 (25.31)</td>
<td>.74</td>
</tr>
<tr>
<td>No CBI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acamprosate × CBI</td>
<td>77.3 (25.37)</td>
<td>79.5 (25.37)</td>
<td>.74</td>
</tr>
<tr>
<td>CBI</td>
<td>77.3 (25.37)</td>
<td>79.5 (25.37)</td>
<td>.74</td>
</tr>
</tbody>
</table>

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Table 4. Participants With ≥1 Heavy Drinking Day During Treatment*

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Intervention</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Main Effects</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>Acamprosate</td>
<td>CBI</td>
<td></td>
</tr>
<tr>
<td>Placebo (n = 618)</td>
<td>433 (70.1)</td>
<td>423 (69.6)</td>
<td>.23</td>
</tr>
<tr>
<td>Placebo (n = 612)</td>
<td>433 (70.1)</td>
<td>423 (69.6)</td>
<td>.23</td>
</tr>
<tr>
<td>Naltrexone</td>
<td>Acamprosate</td>
<td>CBI</td>
<td></td>
</tr>
<tr>
<td>No CBI (n = 607)</td>
<td>419 (68.2)</td>
<td>419 (68.2)</td>
<td>.02</td>
</tr>
<tr>
<td>CBI (n = 619)</td>
<td>433 (70.0)</td>
<td>433 (70.0)</td>
<td>.16</td>
</tr>
<tr>
<td>CBI Interactions</td>
<td>Acamprosate</td>
<td>Naltrexone</td>
<td></td>
</tr>
<tr>
<td>Placebo (n = 309)</td>
<td>207 (67.0)</td>
<td>207 (67.0)</td>
<td>.40</td>
</tr>
<tr>
<td>Placebo (n = 303)</td>
<td>211 (69.6)</td>
<td>211 (69.6)</td>
<td>.40</td>
</tr>
<tr>
<td>Naltrexone</td>
<td>Acamprosate</td>
<td>CBI</td>
<td></td>
</tr>
<tr>
<td>No CBI (n = 307)</td>
<td>204 (68.0)</td>
<td>204 (68.0)</td>
<td>.66</td>
</tr>
<tr>
<td>CBI (n = 308)</td>
<td>219 (71.1)</td>
<td>219 (71.1)</td>
<td>.66</td>
</tr>
</tbody>
</table>

Abbreviation: CBI, combined behavioral intervention.
*Numbers (percentages) of participants with a heavy drinking day at any time during treatment are given for clinical interpretation, but the statistical test is the proportional hazard model of time to the first day of heavy drinking over the 16-week treatment period, adjusting for clinical center and baseline percent days abstinent, fitting all main effects and 2- and 3-factor interactions. See Figure 2 for related hazard ratios and 97.5% confidence intervals.

Table 4. Participants With ≥1 Heavy Drinking Day During Treatment*

Figure 2. Effect Size Estimates and Hazard Ratios for Primary Outcomes

Effect size estimates for percent days abstinent are reported as Cohen d values. Three-way interactions are not shown but all were not significant. CBI indicates combined behavioral intervention; CI, confidence interval.

- **Main Effects**
  - Acamprosate: 0.02 (-0.11 to 0.15)
  - Naltrexone: 0.06 (-0.07 to 0.19)
  - CBI: 0.01 (-0.12 to 0.14)
  - Acamprosate × Naltrexone Interaction: 0.09 (-0.10 to 0.27)
  - Acamprosate/No Naltrexone: 0.01 (-0.17 to 0.19)
  - No Acamprosate/Naltrexone: 0.05 (-0.14 to 0.23)
  - Acamprosate × CBI Interaction: 0.03 (-0.15 to 0.22)
  - Acamprosate/CBI: 0.04 (-0.14 to 0.23)
  - No Acamprosate/CBI: 0.02 (-0.16 to 0.21)
  - Naltrexone × CBI Interaction: 0.07 (-0.11 to 0.25)
  - Naltrexone/CBI: 0.22 (0.03 to 0.40)
  - No Naltrexone/CBI: 0.17 (-0.02 to 0.35)

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,13,33 Cumulative proportion of abstinent 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 Scales29 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.\(^5\) Differential treatment effects were not seen on levels of \( \gamma \)-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 \( \times \) 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 no pills and medical management.
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**

**Relapse to Heavy Drinking.** Overall, all individuals had at least 1 heavy drinking day during the posttreatment period. 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 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 non-significantly 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, non-standardized 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-
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 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., 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 suggesting that naltrexone can be a viable medical management option for treating alcohol-dependent individuals. Although our medical management intervention 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.

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>No. (%)</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>498 (82.5)</td>
<td>488 (78.8)</td>
<td>.13</td>
</tr>
<tr>
<td>Acamprosate</td>
<td>485 (79.8)</td>
<td></td>
<td>.04</td>
</tr>
<tr>
<td>Naltrexone</td>
<td>488 (79.5)</td>
<td></td>
<td>.40</td>
</tr>
<tr>
<td>CBI</td>
<td>495 (81.5)</td>
<td>488 (78.8)</td>
<td>.13</td>
</tr>
<tr>
<td><strong>Interactions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>255 (82.5)</td>
<td>243 (78.6)</td>
<td>.27</td>
</tr>
<tr>
<td>Acamprosate</td>
<td>240 (79.2)</td>
<td>245 (80.3)</td>
<td></td>
</tr>
<tr>
<td>Naltrexone</td>
<td>250 (81.4)</td>
<td>245 (81.7)</td>
<td>.88</td>
</tr>
<tr>
<td>Naltrexone × CBI</td>
<td>239 (76.8)</td>
<td>240 (77.9)</td>
<td>.34</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Drinking Outcomes†</th>
<th>Medical Management (No CBI)</th>
<th>CBI + Medical Management</th>
<th>CBI Only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n = 153)</td>
<td>Naltrexone (n = 154)</td>
<td>Acamprosate (n = 152)</td>
<td>Acamprosate (n = 148)</td>
</tr>
<tr>
<td>Percent days abstinent, mean (SD)‡</td>
<td>59.4 (32.42)</td>
<td>68.1 (31.49)</td>
<td>62.7 (31.47)</td>
</tr>
<tr>
<td>Return to heavy drinking, No. of events (%)§</td>
<td>129 (84.3)</td>
<td>121 (78.6)</td>
<td>123 (80.9)</td>
</tr>
<tr>
<td>Good clinical outcome, No. of events (%)</td>
<td></td>
<td>43 (37.7)</td>
<td>55 (48.2)</td>
</tr>
</tbody>
</table>

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

*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.

**Table 8.** Participants With ≥1 Heavy Drinking Day Over 1 Year Posttreatment*
Although not the main focus of the study, it is notable that the patients receiving the study only CBI had worse outcomes than those receiving CBI and medical management plus placebo pills or medical management plus placebo pills. The “placebo effect” in this trial may have consisted of a combination of factors: a worse outcome secondary to disappointment at not receiving medication in those not receiving pills (negative expectancy effect), optimism about the potential benefits of the medication in those receiving pills (positive expectancy effect), daily pill-taking acting as a reinforcer of motivation, the nonspecific effect of meeting regularly with a medical professional, and the content of the medical management visits themselves. Further evaluation of these issues is anticipated.

It should be noted that the differential treatment effects seen during treatment, while persisting to some degree, largely dissipated over the year post-treatment, consistent with previous reports. While those treated with naltrexone still had less relapse to a heavy drinking day over the year post-treatment, this was only marginally significant. No other significant treatment effect emerged, although there was some indication that those who had received CBI had more abstinent days during the year after treatment. These results suggest that a number of alcohol-dependent individuals require either prolonged or intermittent care. It has been previously suggested that continued naltrexone and medical monitoring, continuation of CBI therapy, or both might be useful approaches for those who do well during initial treatment.

The internal validity of this trial is high, with excellent balance between groups on baseline variables, high medication adherence, complete 16-week drinking data for 94% of the sample, and biological verification of self-report. Potential limits to external generalizability include the intensive research assessments (up to 12 hours), the recruitment and treatment of patients in non-primary care academic settings, exclusion of participants with substantial concurrent psychiatric illness and drug abuse, and the limited time of treatment (16 weeks) given the chronicity and relapse potential in alcohol-dependent individuals. The resulting sample, however, may represent a population of alcohol-dependent patients who could be treated within a medical setting in which health care professionals are in a unique position to intervene, given their ongoing relationships with patients. Post-treatment outcomes will be evaluated further and subsequently reported.

In conclusion, within the context of medical management, naltrexone yielded outcomes similar to those obtained from specialist behavioral treatment (ie, CBI). We found no evidence of efficacy for acamprosate and also no evidence of incremental efficacy for combinations of naltrexone, acamprosate, and CBI. Somewhat unexpectedly, we observed a positive effect of receiving placebo medication and medical management over and above that seen with specialist-delivered behavioral therapy alone. Medical management of alcohol dependence with naltrexone appears to be feasible and, if implemented in primary and other, health care settings, could greatly extend patient access to effective treatment. Future studies that evaluate the usefulness of continued or intermittent care of alcohol-dependent individuals over the longer term should be considered.
PHARMACOTHERAPIES AND BEHAVIORAL INTERVENTIONS FOR ALCOHOL DEPENDENCE


34. Anton RF, Lieber C, Tabakoff B; CDTest Study Group. Carbohydrate deficient transferrin (CDT) and gamma-glutamyltransferase for the detection and monitoring of alcoholics. Alcohol Clin Exp Res. 2002;26:1215-1222.


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