Alcohol Treatment Effects on Secondary Nondrinking Outcomes and Quality of Life: The COMBINE Study*

JOSEPH S. LoCASTRO, PH.D.,† MARSTON YOUNGBLOOD, M.A., M.P.H.,† RON A. CISLER, PH.D.,† MARGARET E. MATTSON, PH.D.,† ALLEN ZWEBEN, D.S.W., L.C.S.W.,† RAYMOND F. ANTON, M.D.,† AND DENNIS M. DONOVAN, PH.D.†

Department of Psychiatry, Boston University School of Medicine and Veterans Affairs Boston Healthcare System, Boston, Massachusetts

ABSTRACT. Objective: To evaluate the full range of alcohol treatment effectiveness, it is important to assess secondary nondrinking outcome dimensions in addition to primary alcohol consumption outcomes. **Method:** We used a large sample (n = 1,226) of alcohol-dependent participants entering the National Institute on Alcohol Abuse and Alcoholism-sponsored COMBINE (Combining Medications and Behavioral Interventions) Study, a multisite clinical trial of pharmacological (naltrexone [ReVia] and acamprosate [Campral]) and behavioral interventions, to examine the effects of specific treatment combinations on nondrinking functional outcomes. We assessed the outcomes at baseline and at the end of 16 weeks of alcohol treatment and again at the 26-week and/or 52-week postrandomization follow-ups. **Results:** (1) Drinking and secondary outcomes were significantly related, especially at the follow-up periods. A higher percentage of heavy drinking days, more drinks per drinking day, and lower percentage of days abstinent were associated with lower quality-of-life measures. (2) All nondrinking outcomes showed improvement at the end of 16 weeks of treatment and most maintained improvement over the 26-week and 52-week follow-ups. Only two measures returned to pretreatment levels at 52 weeks: percentage of days paid for work and physical health. Improvements of nondrinking outcomes remained even after adjusting for posttreatment heavy drinking status. (3) Although nondrinking outcomes showed overall improvement, specific pharmacological and behavioral treatment combinations were not differentially effective on specific secondary outcomes. **Conclusions:** In the current study, changes that resulted from treatment were multidimensional, and improvements in nondrinking outcomes reflected the overall significant improvement in drinking but they were not differentiated between treatment combination groups. Findings from this study support the importance of including secondary nondrinking outcomes in clinical alcohol-treatment trials. (*J. Stud. Alcohol Drugs* **70:** 186-196, 2009)

THE EFFECTIVENESS OF ALCOHOL TREATMENT is typically measured by examining the differences and/or changes in alcohol consumption as the primary outcome dimension (Babor et al., 1994; Finney et al., 2003; Litten and Allen, 1992). However, to test the full impact of alcohol treatment, assessment of secondary nondrinking outcomes has become more frequent in recent clinical trials (Finney et al., 2003; Longabaugh et al., 1994; Maisto and McCollum, 1980; Zweben and Cisler, 1996). Improvements in these areas of life functioning may not necessarily follow solely from changes in alcohol consumption (Longabaugh et al., 1994). Thus, to evaluate the full range of treatment effects, it is important to assess these secondary nondrinking outcome dimensions in addition to primary alcohol consumption outcomes (Cisler et al., 2005).

In a recent review, Donovan et al. (2005) examined the relationship between alcohol dependence and quality-of-life measures (which encompass domains similar to secondary outcome variables of interest in this report). In general, alcohol-dependent patients have lower quality-of-life scores as compared with the norms of the general population (Daeppen et al., 1998; Morgan et al., 2003) and with other medical patients (Foster et al., 1997; Volk et al., 1997). In addition, higher severity of alcohol dependence is predictive of lower quality of life for alcoholics at the beginning of treatment (Morgan et al., 2004).

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†Correspondence may be sent to Joseph S. LoCastro, Psychology Service (116B), VA Boston Healthcare System, 150 South Huntington Avenue, Boston, MA 02130 or via email at: joseph.locastro@va.gov. Marston Youngblood is with the Collaborative Studies Coordinating Center, Department of Biostatistics, University of North Carolina, Chapel Hill, NC. Ron A. Cisler is with the Center for Urban Population Health, University of Wisconsin-Milwaukee, University of Wisconsin School of Medicine and Public Health, and Aurora Health Care, Inc., Milwaukee, WI. Margaret E. Mattson is with the National Institute on Alcohol Abuse and Alcoholism, Bethesda, MD. Allen Zweben is with Columbia University School of Social Work, New York, NY. Raymond F. Anton is with the Center for Drug and Alcohol Programs and the Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina, Charleston, SC. Dennis M. Donovan is with the Alcohol and Drug Abuse Institute and the Department of Psychiatry and Behavioral Sciences, University of Washington, Seattle, WA. A full listing of COMBINE Study staff is available at www.cscc.unc.edu/COMBINE.

The relationships among treatment effects, changes in drinking status, secondary outcomes, and time to follow-up are variable and complex. Alcohol-dependent patients in treatment have shown improvement in several nondrinking outcomes and quality-of-life measures (Foster et al., 1998a,b; Johnson et al., 2004, 2008; Morgan et al., 2003, 2004; Rippeth, 1997). Drinking status during and after treatment appears to mediate the effects of alcohol treatment on these secondary outcomes. For example, those patients who remain abstinent (both long term and short term) show the greatest improvement in quality-of-life measures as compared with those who relapse (Foster et al., 2000b; Mann et al., 1997; Morgan et al., 2004; Rippeth, 1997). Johnson et al. (2004) found that, for subjects taking topiramate (Topamax), there was a relationship between the reduction in percentage of heavy drinking days (PHDD) and improvement in quality of life as well as psychosocial consequences (Johnson et al., 2008). These findings seem to be consistent across different types of single behavioral or pharmacological treatment, although the link between drinking status and secondary outcomes based on the effects of treatment combinations has not been examined in past studies, which is a major goal of the current study. The COMBINE (Combining Medications and Behavioral Interventions) Study provides a rich opportunity to examine the impact of pharmacological and behavioral treatment combinations on multiple nondrinking secondary outcomes assessed at baseline and at the end of the 16-week alcohol-treatment trial and again at the 26-week and 52-week postrandomization follow-ups. The COMBINE Study, sponsored by the National Institute on Alcohol Abuse and Alcoholism, was a multisite, randomized, controlled trial comparing two medications, naltrexone (ReVia) and acamprosate (Campral), evaluated both singly and in combination in the context of two variations of behavioral intervention, one a medical model (medical management) and the other a specialist model (combined behavioral intervention). The current subanalysis includes the 1,226 subjects randomized into an eight-cell factorial design. The COMBINE Study rationale, goals, study design, assessments, and statistical approaches to outcome variables have been reported elsewhere (Anton et al., 2006; COMBINE, 2003; Hosking et al., 2005).

The current study examines several objectives using this large-scale, multisite trial. Assessing improvements in both drinking behavior and nondrinking functioning can inform treatment providers as to overall impact of alcohol interventions on the full range of treatment outcomes. Thus, the overall rationale of the present analysis was to evaluate the importance of including secondary nondrinking outcomes in clinical alcohol-treatment trials and to assess which secondary outcomes are most sensitive to alcohol treatment. A primary goal of the present analysis was to examine whether drinking outcome variables are related to secondary nondrinking outcome variables and whether this relationship is found not only at baseline but also at the end of 16 weeks of treatment and at the 26-week and 52-week postrandomization follow-up periods. Examining longitudinal data provides a more complete clinical picture than does examining only one follow-up period. A second primary goal of the current analysis was to examine whether 16 weeks of alcohol treatment is associated with improvements in secondary nondrinking outcomes and whether specific pharmacological and behavioral treatments and their combinations have differential effects on these outcomes. Also, including 16-week, 26-week, and 52-week follow-up analyses allows for an examination of the temporal effects of treatment on nondrinking outcomes to determine if treatment effects could be sustained over time. As a third objective, this report examined the multiple interrelationships between treatment, alcohol consumption, and nondrinking dimensions of functioning (Longabaugh et al., 1994). Thus, it was anticipated that the effects of treatment combinations on secondary nondrinking outcomes would be associated with drinking status (Cisler and Zweben, 1999). These interrelationships were analyzed at the 16-week, 26-week, and 52-week postrandomization follow-up periods to determine if they were consistent over time. The COMBINE Study provided a unique opportunity to study the temporal effects of treatment and drinking status on nondrinking outcomes by using a design that had advantages over previous studies in this area.

Method

Participant recruitment

The general study methods have been described previously (Anton et al., 2006; COMBINE, 2003; Hosking et al., 2005). Approximately 5,000 participants were recruited by public advertisements, community resources, and from clinical referrals at 11 participating sites across the continental United States, and subsequently were screened by telephone or in person. All in-person screened individuals signed an informed consent form (approved by each site's institutional review board and accompanied by a Certificate of Confidentiality provided by the National Institute on Alcohol Abuse and Alcoholism).

Strict inclusion eligibility criteria were established. These criteria included (1) Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV; American Psychiatric Association, 1994) criteria for alcohol dependence; (2) 4-21 days of abstinence; and (3) more than 14 drinks (females) or 21 drinks (males) per week, with at least 2 heavy drinking days (defined as more than four drinks for females and more than five for males) during a consecutive 30-day period within the 90 days before baseline evaluation. Exclusion criteria included (1) recent history of other substance abuse (other than nicotine or cannabis) by self-report or urine drug screen, (2) psychiatric disorder requiring medication,

(3) unstable medical conditions (e.g., serum liver enzymes more than 3 times normal), (4) more than 7 days of inpatient treatment for substance-use disorders in the 30 days before randomization, (5) taking either study medication within the past month, and (6) planned continued participation in any pre-occurring alcohol treatment during the treatment phase of the study. Subjects were required to have completed any necessary detoxification and 4 days of abstinence before randomization and initiation of study pharmacotherapy.

Participant randomization to treatment conditions

The overall COMBINE Study sample consisted of 1,383 adult participants (428 women and 955 men) who met DSM-IV criteria for alcohol dependence based on the Structured Clinical Interview for DSM-IV (Spitzer et al., 1992). After assessment, participants were randomly assigned to one of nine treatment conditions. All analyses reported in the current study are based on the 1,226 patients randomized to one of eight treatment combinations in which pills (active medications or placebo) were taken by the participants, as detailed in the report of within-treatment outcomes (Anton et al., 2006). A ninth cell (n = 157) of combined behavioral intervention alone (with no pills) is not included in this analysis so as to be consistent with the statistical procedures of the primary COMBINE Study outcome article (Anton et al., 2006). In essence, all subjects were randomized to naltrexone (100 mg/day) or placebo, acamprosate (3 g/day) or placebo, or both medications or placebos along with up to nine sessions of medical management (Pettinati et al., 2004) delivered by a health care professional. In addition to medical management, half of the subjects from each medication group were also randomly assigned to receive a moderate-intensity behavioral intervention, called the combined behavioral intervention (Longabaugh et al., 2005; Miller et al., 2005) delivered by trained and certified counselors. Providers of both combined behavioral intervention and medical management used intervention manuals and were trained by standard protocols (Miller, 2004; Pettinati et al., 2004). The 1,226 study participants had a median age of 44 years; 69% had at least 12 years of education; 46.3% were married or in a stable relationship; 25.1% were separated or divorced; and 28.6% were single or widowed. Ethnic minorities accounted for 23.2% (n = 321) of the randomized sample (n = 1,383), particularly Hispanic (n = 155) and black (n = 109). In the 30 days before randomization, a total of 2.3% of subjects were medically detoxified and 7.7% received inpatient treatment, with no differences between treatment groups.

Assessment: Primary drinking-related variables

For the current article, three drinking-related variables were measured and used as either outcomes or covariates. Using structured interviews from the Form 90 and Form 90 AIR/ED (At Intake, Revised/Economic Data; Miller, 1996; Tonigan et al., 1997), alcohol consumption data were obtained for the three primary drinking outcomes: (1) percentage of days abstinent (PDA), (2) percentage of heavy drinking days (PHDD), and (3) drinks per drinking day (DDD). PDA, PHDD, and DDD were computed using the most recent 30 days of drinking from the 90-day prebaseline assessment window and then again for each consecutive 4-week period. These variables were analyzed at baseline, at the end of the 16-week treatment, and at the 26-week and 52-week postrandomization follow-up periods. The overall completion rates of the Form 90 drinking data at each of the three posttreatment follow-up points (for the total sample of 1,383 subjects) were relatively high, with 94% at Week 16, 91.8% at Week 26, and 88.0% at Week 52. There were no significant differences across the combination treatment groups at any of the three follow-up points. A heavy drinking day was defined as five or more drinks for men and four or more drinks for women per day. A standard drink was 12 oz of beer, 5 oz of wine, or 1.5 oz of 80-proof distilled spirits.

Assessment: Secondary nondrinking variables used in this study

Eleven measures of secondary nondrinking variables were used in the current analyses. The selection of the 11 measures of nondrinking outcomes was based on a procedure that first assessed which domains of functioning were of interest and then selecting one measure for each domain. These data were obtained from structured interviews and self-report questionnaires at baseline and postrandomization Weeks 16, 26, and 52 as follows. Using the Form 90 AIR/ED (Miller, 1996), secondary outcome measures of mutual-help group attendance, and percentage of days paid for work were obtained. Other outcomes included the Brief Symptom Inventory (BSI; Derogatis, 1993); the Perceived Stress Scale (Cohen et al., 1983); the Short Form-12 Version 2 (SF-12v2; Ware and Sherborne, 1992; Ware et al., 2002), which included the physical health aggregate summary and the mental health aggregate summary; and the World Health Organization Quality of Life assessment (WHOQOL-26; Szabo, 1996), which measured the domains of physical health, psychological health, social relationships, and environment. Also, a measure of craving was calculated using the Obsessive-Compulsive Drinking Scale (Anton et al., 1995, 1996).

Data reduction and analyses

All data analysis was performed using SAS Version 8.13 (SAS Institute, Inc., Cary, NC). Pearson correlations were computed to measure associations between each of the 11 secondary variables and the three drinking variables: PHDD, DDD, and PDA. Each set of correlations was calculated

between the drinking and nondrinking variables within each time period (i.e., baseline secondary with baseline drinking variables, 16-week secondary with 16-week drinking variables, 26-week secondary with 26-week drinking variables, and 52-week secondary with 52-week drinking variables).

To analyze the posttreatment improvements of secondary outcomes, a mixed-effects general linear model was used for each secondary variable. Mixed-model estimates (least square means and standard errors) were based on a full model that adjusts for clinical center, each main treatment effect, all two- and three-way interactions, a random individual subject repeated measure, and time period. These models were all comparable and omit adjusting for the baseline value of each secondary variable so that differences could be tested between baseline and each follow-up measurement. Differences between follow-up measures were also calculated (i.e., 16 weeks vs 26 weeks, 16 weeks vs 52 weeks, and 26 weeks vs 52 weeks). All available data were used in the longitudinal analysis of secondary outcomes. To assess whether posttreatment improvements of secondary outcomes were associated with posttreatment drinking status, these models were then recalculated adjusting for the covariate PHDD at Week 16.

To analyze the treatment effects of specific pharmacological and behavioral treatment combinations on specific secondary outcomes, a mixed-effects general linear model was used for each secondary variable to examine the main and interaction effects of three treatments (acamprosate, naltrexone, and combined behavioral intervention; fixed effects) by time (repeated-measures effect) from baseline to end of treatment at 16 weeks (except for WHOQOL, which was assessed at 26 weeks but not 16 weeks) and from baseline to follow-up at 52 weeks (except for the Obsessive-Compulsive Drinking Scale, which was assessed at 26 weeks but not 52 weeks). For each dependent secondary variable, a 2 (Acamprosate/Placebo) × 2 (Naltrexone/Placebo) × 2 (Combined Behavioral Intervention/no Combined Behavioral Intervention) factorial model was fit. The resulting mixed-model estimates for least square means and standard errors are based on a fully saturated model that adjusts for clinical center, each treatment effect, all two- and three-way interaction terms, and baseline value of each secondary variable. To assess whether treatment combination effects were associated with posttreatment drinking status, these analyses were repeated to adjust for the covariate PHDD at Week 16 and at Week 52. Thus, 40 analyses of variance (ANOVAs) were conducted: 11 Secondary Variables × 2 Time Periods (except for the 4 WHOQOL variables at 16 weeks) × 2 Models (unadjusted and adjusted for PHDD). Given the multiplicity of analyses in these related series of hypothesis tests, only those results at the α level $p < .001$ are likely to be truly significant not by chance. Analyses at the nominal $p < .01$ and $p < .05$ were considered as trends only but were not interpreted.

Results

Correlations between drinking and secondary variables by time period

As presented in Tables 1 and 2, the results of the correlations between each secondary variable and the three drinking variables (PHDD, DDD, PDA) indicate that, at baseline, a greater number of significant correlations are seen with the DDD drinking variable (ranging from $r = .08$, $p < .01$, to $r = .25$, $p < .001$) than with the PHDD or PDS variables. However, at the16-week, 26-week, and 52-week assessments all three of the drinking outcome variables are significantly correlated with the secondary outcome variables. For example, in general, a higher PHDD, more DDD, and lower PDA are related to lower quality-of-life measures (SF-12v2 and WHOQOL), and to more psychiatric symptoms (BSI)

Table 1. Correlations between drinking and secondary variables, by time period (baseline and 16-week treatment)

	Baseline drinking variables			16-week drinking variables		
Secondary outcome variables, at baseline or 16 weeks	Percentage heavy drinking days	Drinks per drinking day	Percentage days abstinent	Percentage heavy drinking days	Drinks per drinking day	Percentage days abstinent
Brief Symptom Inventory, global severity	.03	.23‡	.03	.30‡	.32‡	-.22‡
Perceived Stress Scale, total	-.07†	.08†	.10‡	.30‡	.30‡	-.22‡
Percentage days paid for work	.02	-.20‡	-.09†	.02	-.08*	-.05
SF-12 physical health score	-.09†	-.16‡	.05	-.13‡	-.16‡	.08†
SF-12 mental health score	-.01	-.11‡	-.02	-.31‡	-.30‡	.22‡
WHOQOL Physical Health domain	-.06*	-.16‡	.02	–	–	–
WHOQOL Psychological domain	-.00	-.10‡	-.03	–	–	–
WHOQOL Social Relationships domain	.04	-.04	-.06*	–	–	–
WHOQOL Environment domain	.05	-.18‡	-.10‡	–	–	–
Craving, obsessive-compulsive drinking	.18‡	.25‡	-.10‡	.65‡	.37‡	-.66‡
Percentage days of mutual help meetings	-.10	.09	.16†	-.13†	.19†	.17†

Notes: Percentage heavy drinking days, drinks per drinking day, and percentage days abstinent were computed using the most recent 30 days of drinking out of the 90-day prebaseline assessment window and then again for each consecutive 4-week period. Heavy drinking: four or more drinks per day for women and five or more drinks per day for men. SF-12 = Short Form-12; WHOQOL = World Health Organization Quality of Life.

*$p < .05$; †$p < .01$; ‡$p < .001$.

Table 2. Correlations between drinking and secondary variables by time period (26-week and 52-week follow-up)

Secondary outcome variables, at 26 weeks and 52 weeks	26-week drinking variables			52-week drinking variables		
	Percentage heavy drinking days	Drinks per drinking day	Percentage days abstinent	Percentage heavy drinking days	Drinks per drinking day	Percentage days abstinent
Brief Symptom Inventory, global severity	.38‡	.32‡	-.30‡	.43‡	.30‡	-.33‡
Perceived Stress Scale, total	–	–	–	.26‡	.19‡	-.16‡
Percentage days paid for work	-.05	-.22‡	.04	-.07	-.19‡	.01
SF-12 physical health score	–	–	–	-.08*	-.13‡	.03
SF-12 mental health score	–	–	–	-.32‡	-.18‡	.24‡
WHOQOL Physical Health domain	-.30‡	-.26‡	.22‡	-.23‡	-.15‡	.15‡
WHOQOL Psychological domain	-.29‡	-.26‡	.21‡	-.31‡	-.20‡	.20‡
WHOQOL Social Relationships domain	-.21‡	-.21‡	.14‡	-.25‡	-.22‡	.16‡
WHOQOL Environment domain	-.23‡	-.25‡	.15‡	-.21‡	-.24‡	.09†
Craving, obsessive-compulsive total	.64‡	.31‡	-.66‡	–	–	–
Percentage days of mutual help meetings	-.16†	.18†	.20‡	.23‡	.28‡	.27‡

Notes: Percentage heavy drinking days, drinks per drinking day, and percentage days abstinent were computed using the most recent 30 days of drinking of the 90-day prebaseline assessment window and then again for each consecutive 4-week period. Heavy drinking: four or more drinks per day for women and five or more drinks per day for men. SF-12 = Short Form-12; WHOQOL = World Health Organization Quality of Life.
*$p < .05$; †$p < .01$; ‡$p < .001$.

and perceived stress (Perceived Stress Scale). Interestingly, a lower percentage of days paid for work is primarily related to greater DDD (mainly a consumption measure) but not to PHDD or PDA (which includes drinking frequency measures). Thus, the results indicate a temporal shift at posttreatment where lower drinking severity is highly associated with greater psychosocial functioning.

Overall posttreatment improvements (independent of treatment combination groups) in secondary nondrinking outcomes by time period

As shown in Table 3, all secondary outcomes showed significant improvement from baseline to the end of treatment at Week 16. For the four WHOQOL domains (which were not measured at Week 16), there was significant improvement from baseline to the Week 26 follow-up period. Also, significant time differences across the baseline and 16-, 26-, and 52-week time periods indicate that the posttreatment improvements were mostly stable across time. Nearly all secondary outcomes remained significantly improved from baseline to the 26-week and/or the 52-week follow-up time period. Two exceptions to this stability were that the percentage of days paid for work returned to baseline level at the 52-week time point and the SF-12v2 physical health score fell to below baseline at the 52-week time point. However, the interpretation of clinical meaningfulness of the improved outcomes for the SF-12v2 physical health scores is limited because of the small differences of less than 1.0 score between the time points. This is discussed in detail in the Discussion section. From the end of treatment at 16 weeks, three secondary outcomes maintained improvement over the 26-week and/or 52-week follow-up period (i.e., BSI, Perceived Stress Scale, and percentage days of mutual help meetings), whereas two outcomes (SF-12v2 mental health and Obsessive-Compulsive Drinking Scale craving) showed a decline over time but not to the level of baseline. From 26 weeks to 52 weeks, the WHOQOL social relationships and WHOQOL environment domains maintained improvement, whereas the WHOQOL physical health and psychological domains showed an increase over time. All significant differences are at $p < .05$ or less.

In summary, there were significant posttreatment improvements on all secondary outcomes; for most, these changes were maintained over the 26-week and/or 52-week follow-up time periods. These findings demonstrate that non-alcohol-specific secondary outcomes are complex and variable and that alcohol treatment may have a differential impact on these variables.

Overall posttreatment improvements in secondary nondrinking outcomes adjusted for drinking status

To examine whether the significant posttreatment improvements on secondary nondrinking outcomes were associated with posttreatment drinking status, the analyses of posttreatment changes (shown in Table 3) were repeated with the added adjustment of PHDD at Week 16 (data not shown). All significant differences (at <.05) from baseline to Weeks 16, 26, and 52 were nearly identical to the previous analyses (Table 3) that did not adjust for drinking status. Therefore, it appears that the posttreatment improvements and stability of the secondary outcomes remained significant even after adjusting for posttreatment PHDD.

However, this is not to imply that the overall improvements in nondrinking outcomes did not reflect the improvements in drinking outcomes. The COMBINE Study found a substantial overall treatment effect on improved drinking outcomes from baseline to end of treatment and follow-up (Anton et al., 2006; Donovan et al., 2008). Measures of

Table 3. Improvement in secondary outcomes over time (from baseline to 16, 26, and 52 weeks)

Secondary outcome variable	Baseline Adj. mean (SE)	Week 16 Adj. mean (SE)	Week 26 Adj. mean (SE)	Week 52 Adj. mean (SE)
Brief Symptom Inventory, global severity	60.34 (0.30)	52.41[a] (0.37)	52.19[a] (0.40)	51.89[a] (0.41)
Perceived Stress Scale, total	5.79 (0.08)	4.16[a] (0.10)	–	4.32[a] (0.10)
Percentage days paid for work	87.65 (0.75)	91.93[a] (0.61)	89.57[a,b] (0.71)	87.55[b,c] (0.79)
SF-12 physical health score	52.65 (0.24)	53.61[a] (0.21)	–	51.88[a,b] (0.27)
SF-12 mental health Score	41.45 (0.32)	49.44[a] (0.30)	–	48.01[a,b] (0.34)
WHOQOL Physical Health domain	69.99 (0.47)	–	73.29[a] (0.61)	76.85[a,c] (0.54)
WHOQOL Psychological domain	59.38 (0.52)	–	64.44[a] (0.65)	66.08[a,c] (0.61)
WHOQOL Social Relationships domain	56.88 (0.63)	–	65.53[a] (0.68)	65.63[a] (0.68)
WHOQOL Environment domain	63.40 (0.55)	–	69.88[a] (0.58)	69.91[a] (0.58)
Craving, obsessive-compulsive total	25.35 (0.22)	10.10[a] (0.27)	11.91[a,b] (0.31)	–
Percentage days of mutual help meetings	13.37 (1.14)	22.01[a] (1.24)	21.66[a] (1.35)	21.97[a] (1.44)

Notes: Mixed-model estimates (lsmeans) are based on a full model that adjusts for clinical center, each treatment effect, all two- and three-way interaction terms, and time period. SF-12 = Short Form-12; WHOQOL = World Health Organization Quality of Life. [a]Different from baseline mean; [b]different from Week 16 mean; [c]different from Week 26 mean. All significant differences are at $p < .05$.

drinking outcomes from the present study sample assessed at baseline, the end of 16 weeks of treatment, and the 26-week and 52-week follow-up periods were as follows: for PHDD, 65.6%, 16.0%, 21.7%, and 26.4%, respectively; for DDD, 12.5, 7.1, 8.0, and 8.6 drinks, respectively; and for PDA, 25.3%, 74.6%, 67.8%, and 62.7%, respectively. Therefore, both drinking outcomes and nondrinking secondary outcomes are found to improve with treatment and are generally maintained past the end of treatment. However, the results of the present study indicate that, on average, the observed improvements in nondrinking outcomes remain robust even after adjusting for posttreatment drinking status.

Treatment effects of pharmacological and behavioral treatment combinations on secondary outcomes

Preliminary ANOVA of unadjusted baseline values for each secondary variable across the eight treatment-combination groups (Acamprosate × Naltrexone × Combined Behavioral Intervention) found no significant main or interaction effects, thus indicating that the secondary variables were comparable across treatment combinations at baseline. In addition, the prior analyses (Anton et al., 2006; Donovan et al., 2008) of potentially confounding variables assessed at posttreatment indicated that the nine treatment conditions (including the no-pill group) did not differ with respect to the percentage of participants who reported being hospitalized for alcoholism treatment, receiving treatment in an emergency department for alcohol-related reasons, and using medications for drinking, emotional problems, or alcohol detoxification.

To assess the treatment effects of specific pharmacological and behavioral treatment combinations on specific secondary outcomes, 40 ANOVAs were conducted (20 unadjusted for PHDD and 20 adjusted for PHDD). Table 4 summarizes the significance of the main effects and interaction effects of these 40 ANOVAs. Using the $p < .001$ significance level (to account for multiple tests), the results in general indicate that the eight combinations of pharmacological and behavioral treatments did not show great differential effects on the specific secondary outcomes. The only two significant effects reaching the $p < .001$ level were the two-way interactions of Naltrexone × Combined Behavioral Intervention for the SF-12v2 physical health at the 52-week time period for both the PHDD adjusted and unadjusted analyses. These interactions indicated that the combined naltrexone plus combined behavioral intervention group (mean [SE] = 52.1 [0.46] adjusted; mean = 52.2 [0.46] unadjusted) and the drug placebo group with no combined behavioral intervention (mean = 53.1 [0.48] adjusted; 53.1 [0.48] unadjusted) reported higher physical health than the naltrexone/no combined behavioral intervention (mean = 51.0 [0.48] adjusted; 51.0 [0.48] unadjusted) or the combined behavioral intervention/drug placebo groups (mean = 51.0 [0.46] adjusted; 51.0 [0.46] unadjusted). This finding suggests that, together, combined behavioral intervention and naltrexone treatment have a greater impact than either one alone for the SF-12v2 physical health dimension. However, the interpretation of this interaction for the SF-12v2 physical health scale is limited because of the small differences (≤2.1 points) between the groups, which brings into question the clinical meaningfulness for this scale. This is discussed in detail in the Discussion section.

In summary, it appears that the differential treatment effects of specific pharmacological and behavioral treatment combinations on specific secondary outcomes is modest at best, finding few measures with highly significant p values. The hypothesized interrelationships between specific treatment combinations, alcohol consumption, secondary outcomes, and time were not supported. Also, statistical adjustment for multiple hypothesis test comparisons modifies the interpretation of these results. For example, as seen in Table 4, there were other trends toward significance, but these trends did not reach the $p < .001$ criterion and thus were not interpreted.

Table 4. Summary of effects of combination treatments on secondary outcomes of 16-, 26-, or 52-week outcomes: Unadjusted and adjusted for percentage heavy drinking days

	Combination treatment effects at 16, and 26 or 52 Weeks			
Secondary outcome variables	Week 16 Unadjusted PHDD	Week 16 Adjusted PHDD	Week 26 or 52 Unadjusted PHDD	Week 26 or 52 Adjusted PHDD
Brief Symptom Inventory, global severity	NS	NS	NS	NS
Perceived Stress Scale, total[a]	N < P*	NS	NS	NS
Percentage days paid for work	NS	NS	NS	NS
SF-12 Physical Health score[b]	N × C*	N × C*	N × C‡	N × C‡
SF-12 Mental Health score	NS	NS	A × N × C*	NS
WHOQOL Physical Health domain	NS	NS	NS	NS
WHOQOL Psychological domain	NS	NS	NS	NS
WHOQOL Social Relationships domain	NS	NS	NS	NS
WHOQOL Environment domain[a]	NS	NS A × C*	C > No C* A × C†	C > No C*
Craving, obsessive-compulsive total	NS	NS	NS	NS
Percentage days of mutual help meetings	NS	NS	NS	NS

Notes: Mixed-model estimates (lsmeans) are based on a full model that adjusts for clinical center, each treatment effect, all two- and three-way interaction terms, and baseline value of each secondary variable. [a]"<" or ">" defines a main effect in the direction indicated; [b]see Results section for description of N × C‡ interaction. N = naltrexone, A = acamprosate, C = CBI, P = drug placebo, No C = no CBI. All subjects received medical management. SF-12 = Short Form-12; WHOQOL = World Health Organization Quality of Life; NS = no significant main effects or interactions. *$p < .05$; †$p < .01$; ‡$p < .001$.

Discussion

Correlations between drinking and secondary variables by time period

The findings of the present study support the association of drinking status and nondrinking functioning. At baseline, there were a greater number of correlations between the secondary outcomes and drinking variables measuring DDD than those measuring PHDD or PDA. This finding may be a result of the greater impact of the amount of alcohol consumed on any drinking day (primarily DDD) versus the frequency of consumption (primarily PHDD and PDA) on lower nondrinking functioning before treatment. At least at baseline, it was not how often an individual drank but how much was consumed during a drinking day that was associated with secondary outcomes. This may be the case in the COMBINE Study because, at baseline, most individuals were drinking frequently (on average, 75% of the days) but were distinguished by the high levels of consumption, which reached an average of 12.5 DDD. Volk et al. (1997) similarly found, in a sample of primary care patients, that heavy episodic drinkers and those who had frequent heavy drinking reported lower scores on the SF-36 mental health and role functioning domains. They also found that those diagnosed with alcohol dependence reported lower quality-of-life scores, but this was not the case for those diagnosed with alcohol abuse. Using a large probability sample of adults, Okoro et al. (2004) similarly found that heavy episodic and frequent heavy drinking were associated with lower quality-of-life scores than other drinking patterns. A unique feature of the present study is that the association between drinking and secondary outcome measures was also assessed at the end of 16 weeks of treatment and again at the 26-week and 52-week follow-up periods. The results showed similar correlations between secondary outcomes and DDD, but there were also a number of significant correlations between secondary variables and PHDD and PDA. This finding indicates that drinking frequency (primarily PHDD and PDA) as well as quantity (primarily DDD) are important correlates of functioning after treatment, a time at which overall drinking is markedly reduced compared with the pretreatment period. Overall, the correlations at Weeks 16, 26, and 52 were higher than at baseline, which indicated a greater association of drinking status and nondrinking functioning after the end of treatment. One explanation of this finding may be that the most severe alcoholics who, even after treatment, continue to frequently drink heavily with few abstinent days are also those who have the greatest impairment in secondary nondrinking functioning. Some support of this explanation comes from our finding that greater craving (on the Obsessive-Compulsive Drinking Scale) was highly correlated with greater PHDD and lower PDA after treatment and at follow-up. Other studies have also found that the most significant predictor of SF-36 quality-of-life dimensions was severity of alcohol dependence (Morgan et al., 2004) and the Addiction Severity Index (Daeppen et al., 1998). An additional explanation of the higher correlations after treatment is the effect of time in that longer term abstinence may be associated with greater improvement in secondary outcomes (Mann et al., 1997; Morgan et al., 2004). The COMBINE Study similarly found that the overall PDA by the end of follow-

up was about 65% (indicating a substantial improvement in overall abstinence over baseline), which likely influenced the secondary outcomes presented here.

Not all secondary outcome variables were highly associated with all drinking variables. For example, percentage of days paid for work was primarily related to DDD rather than PHDD or PDA across all time points. This suggests that the amount of alcohol consumed, but not the frequency of consumption, may be the most important correlate of work function. This makes sense because heavy episodic drinkers have more social- and work-related difficulties than steady drinkers. Similarly, the SF-12v2 physical health scale generally had lower correlations with all drinking measures as compared with other secondary variables. A reason for this may be that the SF scale measures health functioning (such as pain), which may be more stable and thus less related to variations in drinking than a less severe health measure such as health satisfaction as assessed by the WHOQOL. Others have found similar lack of sensitivity regarding the association of drinking and physical health (Daeppen et al., 1998; Morgan et al., 2004; Stein et al., 1998). This finding of variability in the impact of treatment on certain secondary variables and not others (such as the SF-12v2 physical scale) implies that it may be necessary to select only those secondary outcome variables that have evidence supporting their relevance and their inclusion in alcohol-treatment outcome studies.

Overall posttreatment improvements in secondary nondrinking outcomes by time period

The results indicated that all secondary outcomes showed significant improvement from baseline to the end of 16 weeks of treatment. This finding is consistent with other studies that have found that alcohol-dependent patients in treatment show improvement in several nondrinking outcomes and quality-of-life measures (Foster et al., 1998a,b; Johnson et al., 2004, 2008; Morgan et al., 2003, 2004; Rippeth, 1997).

The unique design of the present study allowed for the examination of whether these changes were stable for up to 52 weeks of follow-up. Nearly all secondary outcomes remained significantly improved from baseline to the 26-week and/or the 52-week follow-up time period. In addition, most of the secondary variables maintained improvement from the end of treatment at 16 weeks to the 26-week and/or 52-week follow-up. The other studies (Foster et al., 1998a,b; Johnson et al., 2004, 2008; Morgan et al., 2003, 2004; Rippeth, 1997) that have also found similar improvement in quality of life after treatment have followed patients for only up to 3-month or 6-month periods. The findings of the present study suggest that the effects of alcohol treatment on nondrinking outcomes can be expected for at least up to 1 year.

Two exceptions to this stability were that the percentage of days paid for work and the SF-12v2 physical health showed improvement at the 16-week end-of-treatment time point but returned to baseline level at the 52-week time point. As previously noted, these two variables showed a lower association with drinking measures across all time periods assessed. It may be that these two variables are not as responsive to improvements in drinking status after treatment. Also, other factors could be more salient than treatment or drinking behavior in accounting for these findings on work and physical health, such as the employment market or severity of health status. Other studies have found that treatment did not produce improvement of SF-36 physical health at the 6-month follow-up (Garg et al., 1999) and produced less improvement in physical health in older patients (Morgan et al., 2004). These findings suggest that the SF-36 physical health scale may not be a sensitive enough measure of treatment impact in alcohol trials. Another consideration is the possible influence of a ceiling effect, which may result in little room for improvement over baseline. In the present study, for example, the percentage of days paid for work was considered quite high (87.65%) at baseline. Also, other studies have found that an alcoholic population shows less impairment at baseline in the SF physical health measure than other functioning (Daeppen et al., 1998; Morgan et al., 2004). This may be the case in the current study, although these normative comparisons were not made.

A very important consideration in interpreting the results of the SF-12v2 physical health scale is the clinical meaningfulness of the change in scores from baseline to the 16-week and 52-week follow-up points. The algorithms (Ware et al., 2002) used to construct the SF-12v2 summary scores produced a Z-transformed normative score mean of 50 and a standard deviation of 10. Ware et al. (2002) note that a 95% confidence interval for the population-based SF-12v2 physical health is 6.6 units and for the SF-12v2 mental health is 9.5. These units are clues to a more meaningful effect at the individual level. As presented in Table 3, the differences in the SF-12v2 physical health scores from baseline to the 16-week and 52-week assessments are less than 1.0. This is less than 0.1 of the standard deviation. Therefore, although these differences are statistically significant, it is questionable if this small a difference is clinically meaningful. Again, these findings from the current study raise the question whether the SF-12v2 physical health scale is a sensitive enough measure for inclusion in alcohol-treatment trials. In contrast, the SF-12v2 mental health difference between baseline and 16 weeks is 7.99, and between baseline and 52 weeks it is 6.56, which provides more confidence in the clinical meaningfulness of these significant improvements.

A noteworthy finding of the present study is that all five measures of mental health and social functioning (BSI, Perceived Stress Scale, WHOQOL psychological domain, WHOQOL social relationships, and SF-12v2 mental health) showed significant improvement after treatment and maintained the improved level from baseline to the 52-week

follow-up time period. This finding underscores the importance of having a multidimensional assessment in alcohol-treatment trials. It shows that, alone, drinking cannot account for differences in outcomes in a heterogeneous alcohol population. Other studies have emphasized the positive effects of treatment on psychological and role functioning (Foster et al., 2000a; Garg et al., 1999). These findings may be a consequence of the greater deficit of psychological functioning at baseline (Morgan et al., 2003, 2004; Smith and Larson, 2003) and thus a greater potential impact of treatment in these areas of functioning. Also, the current study found a greater attendance after treatment at mutual help meetings such as Alcoholics Anonymous, which may have helped maintain the psychosocial gains.

One limitation to the overall interpretation of the duration of improvement on the range of secondary measures is the missing assessments of these domains from some study participants at the end of the 52-week posttreatment follow-up. Although we had assessments of 90% of the study participants, it is quite likely that those for whom we did not have assessments had poorer outcomes on a variety of secondary measures. Another limitation is that the observed overall improvements may be the result of other factors in addition to the treatment intervention, such as study participation or readiness to change.

Are overall posttreatment improvements in secondary nondrinking outcomes associated with posttreatment drinking status?

The results of the present study indicated that the improvements and stability found with the secondary outcomes remained significant even after adjusting for the posttreatment measure of PHDD. These improvements in secondary outcomes seem to reflect the improvements found in drinking outcomes, but the findings suggest that they may not be totally accounted for by posttreatment drinking status.

The findings of this study present a more complex picture than those of other studies that have examined treatment improvements in secondary outcomes. In one of the largest studies, Morgan et al. (2004) found that the greatest level of improvement in the SF-36 scores was in a subsample of individuals who had remained continuously abstinent across a 6-month period. These results may not be directly comparable to those of the present study, because the Morgan et al. (2004) study was a within-treatment design in which subjects received open-label acamprosate plus behavioral therapy during all 6 months without any follow-up assessment. Another medication study has found a within-treatment (14-week) relationship between the reduction in PHDD and improvement in quality-of-life measures (Johnson et al., 2004) and psychosocial consequences (Johnson et al., 2008). Other studies have also found that those patients who relapse after treatment show a decrease in quality-of-life measures compared with those who remain abstinent (Foster et al., 1998b, 2000a; Mann et al., 1997; Rippeth, 1997). However, not all studies have shown the association between continued abstinence and improvement in functioning. Donovan et al. (2005), in a review of quality-of-life outcomes in alcohol-treatment studies, point out that some researchers (Maisto and McCollum, 1980; Pattison, 1976; Pattison et al., 1977) do not assume that changes in drinking status are predictive of changes in nondrinking functioning. Foster et al. (1998a) found no association between time to relapse and secondary outcomes. In a subsequent study, Foster et al. (2002) found change in alcohol consumption but no corresponding improvement in nondrinking areas of functioning. Also, Morgan et al. (2003) found that substance use during treatment was not related to end-of-treatment quality of life. These studies that relate improvements in drinking status and secondary functioning are difficult to compare owing to great variations in duration of treatment, time to follow-up, and measurement of nondrinking outcomes. Also, the discrepancies in these studies are difficult to explain because of the inherent problem of determining which areas of functioning are directly a consequence of drinking versus which areas are related to general functioning and satisfaction with life (Longabaugh et al., 1994).

In addition, the time to resumption of drinking after treatment may determine its impact on secondary outcomes. For example, if patients relapse later in their recovery, their psychological and social improvements may have already been well established and thus will be affected less by their late relapse, whereas patients who experience an early relapse may have had less opportunity to establish changes in their functioning. Therefore, it is difficult to determine the cause and effect of drinking and other areas of functioning. For example, Miller et al. (1983) suggested that those who had less reduction in alcohol consumption after treatment continued to have life problems. Further research is needed to discover a common variable, or a series of variables in a causal chain, that may link drinking and nondrinking outcomes.

Treatment effects of pharmacological and behavioral treatment combinations on specific secondary outcomes

The COMBINE Study design allowed the examination of whether specific pharmacological and behavioral treatment combinations had differential effects on nondrinking measures of functioning. It also allowed for an exploration of the complex interrelationships between the effects of specific treatment combinations at various times after treatment, alcohol consumption, and secondary nondrinking outcomes.

The results of the present study provided little, if any, support for these complex hypothesized interrelationships. Only one interaction of treatment combinations, the Naltrexone × Combined Behavioral Intervention interaction for the SF-12v2 physical health, reached the statistical significance of

$p < .001$ adjusted for multiple comparisons. It is difficult to interpret the clinical meaningfulness of this finding. As previously noted, the 95% confidence interval for the SF-12v2 physical health scale is 6.6. The differences between the four groups in this interaction were no larger than 2.1 and therefore do not suggest clinically meaningful differences for this scale.

The present study's lack of strong positive findings regarding the effects of specific treatment combinations on nondrinking outcomes may be the result of the high level of overall improvement seen in both drinking and nondrinking measures for all subjects regardless of treatment assignment, including the placebo groups. Because other studies have not examined differential effects of specific kinds of treatments on drinking status and secondary outcomes, it is difficult to directly compare the results of the present study with other studies in the current literature. For example, an open-label study of acamprosate (Morgan et al., 2004) and a clinical trial of topiramate (Johnson et al., 2004, 2008) included within-treatment assessments only and no posttreatment follow-up. In addition, as in other longitudinal studies, there is the potential for self-selection bias in those who continued to participate in follow-up research assessments (i.e., 1,226 randomized vs 1,107 remaining at the last follow-up).

Conclusions

The results of the present study support the importance of including secondary nondrinking outcomes in clinical alcohol-treatment trials. Assessing the full range of improvements in both drinking behavior and dimensions of functioning and quality of life can inform treatment providers and policy makers as to the types of treatment programming needed. Although the present study found no differences among the specific types of treatment combinations in regard to effects on particular areas of functioning, it clearly demonstrates overall improvement in nondrinking functioning. Changes resulting from treatment are multidimensional, and improvement in both drinking and nondrinking outcomes may reflect each other in complex ways. This report only begins to examine the varied interrelationships among treatment, alcohol consumption, and nondrinking dimensions of functioning over time. Given the importance of achieving improvement in both drinking and functional status when treating alcohol dependence, future research should focus on developing a generally accepted and standardized model of measuring these domains so the processes and temporal aspects of recovery and relapse can be more clearly understood.

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