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Testing Combined Pharmacotherapies and Behavioral Interventions in Alcohol Dependence: Rationale and Methods

The COMBINE Study Research Group

Increasing knowledge about effective therapies for alcohol dependence calls for new research designs to examine treatment interactions between pharmacotherapies and behavioral interventions. In 1997, the National Institute on Alcohol Abuse and Alcoholism recruited 11 sites and a coordinating center for a large-scale (1,375 subjects), randomized placebo controlled trial to test 16 weeks of active treatment using naltrexone and acamprosate alone and in combination. Most participants receive 9 brief sessions delivered by medically trained providers to promote sobriety and enhance medication adherence (Medical Management, MM). Half the participants are also randomized to individualized psychotherapy (up to 20 sessions of Combined Behavioral Intervention, CBI), integrating elements of the successful behavioral interventions from Project MATCH. COMBINE seeks to evaluate the efficacy of the two most promising medications (naltrexone and acamprosate) both singly and together, when combined with different intensities of behavioral therapies. COMBINE incorporates a number of innovative design aspects, including a no-pill psychotherapy-alone condition, behavioral interventions that are both manual-guided and individualized, and pharmacotherapy dosing that is greater than in some previous trials. Two COMBINE pilot studies demonstrate the safety and acceptability of the combination pharmacotherapy dosing, and the feasibility of implementing the manualized behavioral interventions. This paper introduces COMBINE's goals, methods and analytic strategies, and their potential to improve multimodal treatment selection.

Key Words: Alcohol-Dependence, Pharmacotherapy, Behavioral-Intervention, Methodology.

BACKGROUND AND RATIONALE

History of the COMBINE Project Funding Initiative

Behavioral and pharmacologic research supported by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) has contributed to significant advances in treatment. Three events over the last decade prompted NIAAA to initiate a multi-site study combining both modalities in a single trial: 1) Naltrexone was approved for the treatment of alcohol dependence in 1994; 2) Project MATCH produced and tested three manual-guided behavioral interventions; and 3) acamprosate proved to be effective in several European studies, prompting its manufacturer to initiate the process of obtaining FDA approval. In 1997, NIAAA issued a Request for Applications (RFA) to encourage testing naltrexone and acamprosate alone and in combination with two different behavioral interventions. Following a competitive review, 11 clinical sites and one Coordinating Center were funded to design and conduct a randomized clinical trial (RCT). The purpose of this paper is to describe the rationale and methods for this trial, which was entitled COMBINE, a study testing combined pharmacotherapies and behavioral interventions in alcohol dependence.

STUDY OBJECTIVES

Mandate

The goal of COMBINE is to determine if improvements in treatment outcome for alcohol dependence can be achieved by combining pharmacotherapy and behavioral interventions. COMBINE seeks to evaluate the efficacy of the two most promising medications (naltrexone and acamprosate), both singly and together, when combined with different intensities of behavioral treatment. One behavioral intervention employs brief sessions that are focused on enhancing medication adherence and abstinence. The second behavioral intervention is a more intensive treatment that combines a series of successful features from interventions that have been previously evaluated. The brief session therapy is intended to approximate a type of treatment that might be suitable for delivery in primary care settings. The more intensive therapy is suitable for

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The members of the COMBINE Study Research Group are listed in the Appendix.

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delivery by trained psychotherapists working in specialized alcoholism treatment facilities.

STUDY TREATMENTS

General Principles for Treatment Selection

Pharmacological Treatments In the past several years, there has been increasing interest in the use of pharmacotherapy for alcohol dependence (Chick 1996; Garbutt et al., 1999; Kranzler 2000a; Litten and Allen, 1991; Litten and Allen, 1998; Litten et al., 1996). The development of effective pharmacotherapies has improved the treatment of other mental disorders, such as schizophrenia, mood disorders and anxiety disorders, and of other addictive disorders, such as nicotine dependence and opioid dependence. The development of agents that can reduce the intake of alcohol and assist with initiating and/or maintaining abstinence could have a similar impact on improving treatment for alcohol dependence.

Two medications, naltrexone and acamprosate, have each shown efficacy in the treatment of alcohol dependence in placebo controlled clinical trials conducted in the U.S. and Europe. For most of these studies, alcohol dependent persons received a behavioral treatment to which the active medication or placebo was added; the amount of drinking or proportions of patients remaining abstinent are compared over time between the placebo and medication groups. Naltrexone has been approved for the treatment of alcohol dependence by the U.S. Food and Drug Administration (FDA) since 1994 and is approved in several European countries and Australia. Acamprosate is currently approved throughout most of Europe and South America, Australia, and parts of Asia and Africa for the treatment of alcohol dependence and is currently under FDA review in the U.S. (Mason and Ownby, 2000).

Naltrexone. Naltrexone is an opioid antagonist that is primarily selective for the mu-opioid receptors. Brain opioid systems are important in mediating alcohol consumption (George et al., 1991; Koob, 1992; Tabakoff and Hoffman, 1983). The administration of mu-opioid agonists to animals increases alcohol consumption (Reid and Hubbel, 1987; Wild and Reid, 1990). In contrast, in several animal species (rats, mice and nonhuman primates), administration of mu-opioid receptor antagonists, such as naltrexone, generally reduces alcohol consumption (Froelich et al., 1990; Hemby et al., 1997; Kornet et al., 1991; Volpicelli et al., 1986). In humans, opioid antagonists such as naltrexone are reported to reduce the positively reinforcing, pleasurable effects of alcohol (Swift et al. 1994; Volpicelli et al. 1995); to increase the aversive effects of alcohol (Swift et al. 1994); and to suppress craving for alcohol (Davidson et al., 1999; Monti et al., 1999; Roberts et al., 1999; Volpicelli et al., 1992). The effects of opioid antagonists to decrease alcohol consumption may be mediated through an interaction with dopamine systems. It is hypothesized that activation of dopamine pathways in the ventral tegmentum and nucleus accumbens mediates drug reward and is responsible for the dependence-producing properties of all drugs of abuse (Wise and Bozarth, 1987). In animals, ethanol administration increases dopamine release in these areas of the brain (Gessa et al., 1985); this action is blocked by opioid antagonists (Benjamin et al., 1993).

Several clinical trials with naltrexone have demonstrated its efficacy in the treatment of alcohol dependence (Kranzler and Van Kirk, 2001; Monti et al., 2001; Morris et al., 2001; O'Malley et al., 1992; Volpicelli et al., 1992) but not all (Kranzler et al., 2000b; Krystal et al., 2001; Chick et al., 2000a; Heinala et al., 2001) –although some showed effects of naltrexone on secondary analysis (Chick et al., 2000a; Heinala et al., 2001). A randomized clinical trial of 70 alcohol-dependent veterans receiving day-treatment followed by group outpatient therapy found reduced craving and drinking in subjects receiving naltrexone compared to a placebo group (Volpicelli et al., 1992). A randomized, double blind placebo controlled trial of 50 mg daily naltrexone in 131 abstinent alcoholics receiving cognitive behavioral therapy showed increased percent days of abstinence and delayed onset of heavy drinking in the naltrexone group (Anton et al., 1999; Anton et al., 2001a; Anton et al., 2001b). A double blind placebo-controlled study of 97 male and female alcoholics receiving naltrexone or placebo and either individual coping skills/relapse prevention therapy or supportive therapy found that the naltrexone treated groups drank on fewer days, consumed fewer drinks in total and had a delayed onset of heavy drinking. (O'Malley et al., 1992). Of interest, a medication-psychotherapy interaction was observed in this clinical trial. Naltrexone significantly improved the percent of subjects with continuous abstinence receiving the supportive psychotherapy but not for those receiving the coping skills psychotherapy. Yet, for subjects taking naltrexone who drank, those receiving coping skills therapy were less likely to drink heavily than those receiving supportive therapy. Another trial has shown an interaction in which optimal benefit occurred with naltrexone and coping skills therapy (Heinala et al., 2001). Finally, the question of ongoing benefits after naltrexone cessation has been tested in two studies, which found that although naltrexone treated individuals continued to do better on average than placebo treated participants, the magnitude of the difference declined over time (Anton et al., 2001a,b; O'Malley et al., 1996).

Very little work has been done to establish the optimal dose of naltrexone, with most studies testing the 50 mg daily dose. However, preclinical studies have demonstrated that the suppressive effects of naloxone and naltrexone on alcohol self-administration are dose-dependent (for a review, see O'Malley and Froehlich, 2003), and the possibility that higher doses may be more effective in human subjects is suggested by clinical experience and the preliminary results of a clinical trial by McCaul and colleagues (Litten and Fertig, 1996) and a controlled laboratory study by the same group (McCaul et al., 2000a,b). In addition, higher

doses may provide greater protection against the effects of missed doses. For these reasons, COMBINE is testing 100 mg daily.

Acamprosate. Acamprosate (calcium acetylhomotaurine) is a structural analogue of taurine, and has modulatory effects at n-methyl-d-aspartate (NMDA) receptors (Littleton and Little, 1994). As alcohol withdrawal is associated with reduced GABAergic inhibition and increased glutamatergic excitation, a reduction of postwithdrawal neuronal hyperexcitability by acamprosate may result in reduced physiologic and psychological distress and thus reduced desire for alcohol (Littleton, 1995; Popp and Lovinger, 2000).

Chronic administration of acamprosate reduces alcohol consumption in animal models of excessive alcohol consumption. Rats trained to drink alcohol daily show increased consumption when alcohol is made available after a period of deprivation; this paradigm has been proposed as an animal model of relapse (Diana et al., 1996). Chronic acamprosate administration significantly attenuates the increased alcohol consumption induced by depriving alcohol drinking rats from alcohol for 5 days and then reinstating alcohol (Heyser et al., 1998). In most of the 16 placebo-controlled clinical trials of acamprosate for the treatment of alcohol dependence conducted in Europe, acamprosate significantly increased the proportion of patients that remained continuously abstinent (Chick et al., 2000b; Lhuintre et al., 1990; Mason and Ownby, 2000; Mason and Ownby, 2002; Sass et al., 1996; Whitworth et al., 1996) and a U.S. multicenter randomized controlled trial has found acamprosate superior to placebo in a motivated subset of the participants (Mason, 2001). Based on evidence that the effectiveness of acamprosate is dose dependent (for a review, see Mason and Ownby, 2000; Mason, 2001; Paille et al., 1995), COMBINE elected to test a 3 g daily dose. In addition, attrition has been an issue in some studies, highlighting the need for vigorous follow-up and intent-to-treat analyses.

Combination Pharmacotherapy. There are three important reasons for combining these two particular medications in a treatment study for alcohol dependence. Naltrexone and acamprosate have very different mechanisms of action and presumably target different aspects of the alcohol dependence syndrome. First, naltrexone acts on endogenous opioids and midbrain DA activity to reduce the rewarding effects of alcohol (Hemby et al., 1997; Koob, 1992). Acamprosate modulates alcohol-withdrawal induced increases in midbrain DA (Foster Olive et al., 2002). Hence, the net effect of combining naltrexone and acamprosate may be to modulate the neurochemical effects responsible for triggering drinking or conditioned responses to drink even after a prolonged period of abstinence. Second, while naltrexone reduces craving for alcohol that is driven by positive reinforcement (Volpicelli et al., 1995), acamprosate diminishes the negative reinforcement of conditioned craving that follows cessation of drinking (Spanagel and Zieglgansberger, 1997). It is therefore reasonable to predict that the combination of naltrexone and acamprosate might make it easier both to abstain and to prevent a 'slip' from turning into a relapse. Third, this medication combination has the potential to provide an increased level of efficacy (either additive or synergistic) without increased intensity of side effects because of the two medications' different neurochemical actions (Mason, 2001). As a result, the combined use of these two medications may yield a more effective treatment. Acamprosate may be particularly useful in helping participants avoid initial alcohol consumption and enhancing treatment retention by attenuating protracted alcohol withdrawal. Naltrexone may be particularly efficacious in reducing the likelihood of heavy drinking following a slip.

In COMBINE, agents are provided to subjects in blister packs with sections divided into morning, noon, and evening administration to maximize adherence. Naltrexone is provided in two capsules to be taken each morning, as 25 mg for the first three days, 50 mg for the next four days, and 100 mg per day thereafter. Acamprosate is provided in 500 mg pills, as two pills to be taken three times per day, for a total of 3 g. The two agents have distinct appearances and for each active agent, a placebo of identical appearance is used, and subjects are given no instructions or indication as to the identity of either agent-placebo pair.

Behavioral Interventions

Recent pharmacotherapy efficacy studies in alcohol dependence have generally employed intensive psychotherapies delivered by trained therapists. There is now a strong trend, however, for alcoholics to be treated within a managed care setting (Garnick et al., 1994) where the number of sessions is limited and usually provided by staff without specialized training in addiction treatment. Hence, for both scientific and practical reasons, it is important to determine if pharmacotherapy has differential efficacy depending on the type of counseling or psychotherapy with which it is combined. Extrapolation from O'Malley and colleagues' (1992) studies in which no clear advantages were observed between supportive therapy and the more intensive cognitive behavioral therapy may provide limited information, since both therapies were delivered in equal time by trained therapists. Hence, the effective 'dose' of psychotherapy between both treatments may have been similar. An important challenge is, therefore, to define the optimal 'dose' of psychotherapy treatment (Howard et al., 1986) both alone and in combination with treatment medications. COMBINE has developed two approaches to behavioral interventions that offer a degree of contrast between what may be feasible in the primary care environment and an alcohol dependence specialty treatment model, viz. Medical Management and Combined Behavioral Intervention.

Medical Management (MM). MM is a manualized treatment (Pettinati et al., 2000) designed to approximate a

primary care approach to alcohol dependence. The treatment, delivered by a medical professional (i.e., nurse or physician), provides strategies to increase medication adherence (Volpicelli et al., 1997) and supports abstinence through psychoeducation and referral to groups such as Alcoholics Anonymous (Barrett and Morse, 1998; Carty et al., 1998; Emrick et al., 1993). The initial session, lasting 40–60 min, involves: reviewing the alcohol dependence diagnosis and negative consequences from drinking, a recommendation to abstain, medication information, strategies to enhance medication adherence, and referral to support groups such as Alcoholics Anonymous. In subsequent 15–25 min visits, assessment includes drinking, overall functioning, medication adherence, and side effects. Session structure varies according to drinking status and treatment compliance. When nonadherence occurs, the clinician evaluates the reasons and helps patients devise plans to enhance medication adherence. Patients who drink are urged to attend support groups and are given common sense recommendations, such as avoiding bars. Patients who discontinue medication because of intolerance are seen for a monthly 15–25 min "Medical Attention" meeting, which employs a similar approach, focusing on drinking and overall health. In the event of side effects, procedures are specified for the use of concomitant medication to ameliorate side effects or dose reduction of either or both study agents, as well as resumption of study agents if side effects remit.

Combined Behavioral Intervention (CBI). CBI was designed to be a state-of-the-art individual outpatient psychotherapy for alcohol dependence. It merges a variety of well-supported treatment methods into an integrated approach. A manual-guided therapy, CBI nevertheless allows for normal clinical flexibility and true individualization of treatment (Miller et al., 2003). CBI builds upon features in the manualized therapies of Project MATCH (Kadden et al., 1995; Miller et al., 1994; Nowinski et al., 1995; Project MATCH Research Group, 1993) and provides skills training and support system involvement that follows what has been described as a community reinforcement approach to treatment (Azrin et al., 1982; Meyers and Smith, 1995). It is organized in four phases:

Phase 1, focused on building motivation for change, begins with a single session of motivational interviewing (Miller and Rollnick, 1991), which is the general clinical style to be used throughout CBI. This is followed by client assessment feedback in the style of Motivational Enhancement Therapy (Miller et al., 1994).

Phase 2 includes a functional analysis of drinking, a review of psychosocial functioning, and a survey of the client's strengths and resources, all designed to be used in development of an individual plan for treatment and change. Whenever possible, a supportive significant other, defined in terms of the relationship's value, investment, and willingness, is then engaged, and participates in the client's treatment sessions with a frequency ranging from a few to all sessions, to facilitate compliance and abstinence and reinforce as many of the CBI modules as the relationship seems to warrant. The merits of an abstinence goal are emphasized, and each client is encouraged to become involved in a 12-step or other mutual-help group.

Phase 3 draws upon a menu of nine cognitive-behavioral skill-training modules chosen on the basis of the client's needs as clarified during phase 2 (cf. Kadden et al., 1995). The modules include: 1) assertiveness skills, 2) communication skills, 3) coping with craving and urges, 4) drink refusal and social pressure, 5) job finding, 6) mood management, 7) mutual help group facilitation, 8) social and recreational counseling, and 9) social support for sobriety. All modules involve specific behavioral coaching and skill practice.

Finally, *phase 4* involves maintenance check-ups in which therapist and client review progress to date, renew motivation for change, and reaffirm commitment to an original or revised change plan. CBI also includes a set of eight optional "pull-out" procedures that can be used at any appropriate point during treatment: 1) sobriety sampling, 2) raising therapist's concerns, 3) implementing case management, 4) handling resumed drinking, 5) supporting medication adherence, 6) responding to a missed appointment, 7) telephone consultation, and 8) crisis intervention.

The number, frequency, and duration of CBI treatment sessions are negotiated between therapist and client, within the bounds of 20 sessions and 16 weeks. Although delivered mostly in weekly 50-min outpatient visits, CBI sessions can also occur more often than weekly (particularly at the outset), and can be phased down to biweekly or less frequent sessions (especially in phase 4). Therapists are guided by a comprehensive CBI manual (Miller et al., 2003), using checklists to ensure that proper procedures are included within each offered module. A variety of client handouts and worksheets are also provided to enhance consistency of practice.

STUDY DESIGN

Patient Population

A total of 1,375 subjects meeting the American Psychiatric Association's Diagnostic and Statistical Manual-Fourth Edition (DSM-IV) criteria for alcohol dependence are to be recruited from 11 sites (see appendix)(American Psychiatric Association, 1994). Eligibility criteria are summarized in Table 1. Subjects are recruited who acknowledge a desire to stop drinking. Important exclusion criteria include recent opiate use or past 6 month opiate abuse or dependence disorder, or active dependence disorder with any other substance other than cannabis or nicotine, serious psychiatric disorder requiring specific pharmacological intervention, medical conditions that are unstable or for which either of the study medications are contraindicated (including liver function tests more than 3 times normal), and having received one or the other study medication

Table 1. COMBINE Eligibility Criteria

Inclusion Criteria	Exclusion Criteria
1. Male and Female outpatients 18 years of age.	1. Participants who meet current DSM-IV criteria for bipolar disorder, schizophrenia, bulimia/anorexia, dementia, or a psychological disorder requiring medication.
2. Participants will have a current DSM-IV diagnosis of alcohol dependence.	2. Participants requiring concomitant therapy with any medications that pose safety issues (see Appendix B).
3. Participants will have signed a witnessed informed consent.	3. Participants with a current diagnosis of dependence on any drug except for nicotine, cannabis, and alcohol, or habitual caffeine use. If there is a positive urine screen the participant can be retested after the (metabolic) interval appropriate to that drug. If the second urine drug screen is positive the person is excluded.
4. Participants must have been drinking a minimum of ≥14 drinks (females) or ≥21 drinks (males) on average per week over a consecutive 30-day period in the 90-day period prior to initiation of abstinence, and have two or more days of heavy drinking (defined as 4 drinks for females and 5 drinks for males) in the 90-day period prior to initiation of abstinence.	4. Participants who meet DSM-IV criteria for opiate dependence or abuse within the past 6 months, chronic treatment with any opiate-containing medications during the previous month, or urine positive for opioids.
5. Participants must have had a minimum of 4 consecutive days (96 hours) of abstinence and have a CIWA < 8 prior to randomization.	5. Participants who have significant medical disorders that will increase the potential risk of study treatment or interfere with study participation, and participants with sensitivity to study medications or related drugs as evidenced by adverse drug experience, especially with opiate-containing analgesics, opioid antagonists, or acamprosate.
6. Participants can be abstinent for a maximum of 21 days prior to randomization.	6. Participants with abnormal AST or ALT (more than 3 times the upper limit of the normal range (ULN)) or elevated bilirubin (more than 10% above the ULN). Tests may be repeated if initial results are out of range.
7. Participants will have no more than 21 consecutive days of planned absence during the 16 week active treatment period.	7. Participants who are pregnant or nursing infant(s), and women of childbearing potential not using a contraceptive method judged by the investigator to be effective.
8. Participants who are able to identify at least one "locator" person to assist in tracking the participant for follow-up assessment.	8. Participants who intend to engage in additional formal treatment for alcohol-related problems, or who intend to continue in current treatment for alcohol-related problems during the active treatment period. Self-help treatments are not considered formal treatment.
9. Participants who are able to speak and understand English.	9. Participants who have had more than seven days of inpatient treatment for substance use disorders in the 30 days previous to randomization.
	10. Participants who have prior use of study medication(s) in the last 30 days.

within the past 30 days. Subjects need to have been drinking a minimum of 14 drinks (females) or 21 drinks (males) on average per week over a consecutive 30-day period in the 90-day period prior to initiation of abstinence. They also need to have two or more days of heavy drinking (defined as 4 drinks for females and 5 drinks for males) in the previous 90 days with the last drink being within 21 days of randomization to treatment. Prior to randomization and initiation of study pharmacotherapy, all subjects must complete any needed detoxification and four days of abstinence from alcohol.

Recruitment Considerations

Participants are recruited from inpatient and outpatient referrals within the study sites and the community and media sources. During the pilot study, external sources and media advertisements generated the most telephone contact with study personnel. Subjects must produce a breath alcohol level of zero prior to completing consent and baseline measures.

Treatment Conditions

After assessment (see below), subjects are randomly assigned to one of nine treatment conditions (see Fig. 1), using a permuted block randomization procedure, with varying block sizes. This will result in approximately 153 subjects per cell. Subjects in one cell (termed "cell 9") receive no study medication capsules (active or placebo) or MM intervention but only CBI therapy. This cell is included to contrast the effects of pill taking (Barlow et al., 2000) on the outcome achievable with CBI alone (i.e., comparing cells 5 and 9).

Treatment Durations, and Frequencies

Subjects receiving study medication are all offered 9 Medical Management (MM) appointments (weeks 0, 1, 2, 4, 6, 8, 10, 12, and 16). Subjects who receive CBI have a maximum of 20 sessions over a total of 16 weeks of treatment study participation. They are also evaluated by research assistants on the Medical Management session days for drinking history and craving. On weeks 8 and 16 a

Medical Management (MM)

	Placebo	Acamprosate
Placebo	1	2
Naltrexone	3	4

Medical Management (MM) + COMBINE Behavioral Intervention (CBI)

	Placebo	Acamprosate	No Pills
Placebo	5	6	
Naltrexone	7	8	
No Pills			9

Fig. 1 COMBINE Treatment Combinations. Participants are randomly assigned to treatment by a stratified random block design controlling for clinical center. The medication aspects of the study are double-blind and double-dummy (i.e., all medication participants receive capsules for either: dual placebo (cells 1 and 5), naltrexone 100 mg per day plus placebo acamprosate (cells 3 and 7), acamprosate 3 g per day plus placebo naltrexone (cells 2 and 6), or both active pharmacotherapies (cells 4 and 8). Medications are provided in three divided doses per day.

longer assessment (see below) is performed. After week 16, treatments stop but subjects are followed for the next 52 weeks and seen in person on weeks 26, 52, and 68 (following randomization) for drinking history and other assessments. Subjects assigned to both behavioral interventions receive 9 MM and up to 20 CBI sessions. Subject termination from the treatment portion of the protocol may result for a variety of reasons, most often adverse events, poor treatment response, or lack of participant interest; all subjects who terminate prematurely undergo an end-of-treatment evaluation, and are encouraged to attend research follow-ups.

ASSESSMENT

Major Considerations

The primary function of the assessment process in the trial is to evaluate the efficacy of the interventions and to monitor their safety. A number of considerations underlie the assessment process and the choice of specific measures (Connors et al., 1994). First, it is necessary to develop a brief screening instrument that can be used over the phone or in person to determine whether or not a potential subject meets the basic inclusion/exclusion criteria. Second, it is necessary to assess physical health and liver function since these can be affected by the trial medications and can affect medication adherence. These measures, as well as medication levels, side effects, and adverse events are to be monitored across time to ensure participants' safety. Third, measures of the efficacy of the pharmacotherapies and behavioral therapies are needed. The primary outcome measures are related to drinking behavior: 1) percent days abstinent, and 2) number of days to first heavy drinking episode (5 or more drinks per day for males, 4 or more for females). Additional drinking-related measures serve both as potential baseline covariates and as secondary substance-related outcome measures, such as: level of craving, presence of a DSM-IV diagnosis of alcohol dependence, biological markers of heavy alcohol consumption (e.g., carbohydrate deficient transferrin) (Anton et al., 2001a), number of heavy drinking days, use of other drugs, self-efficacy, motivation and readiness to change, network support for drinking (Longabaugh et al., 1998), and a composite outcome measure that integrates both alcohol consumption and alcohol-related problem variables. Fourth, participants' emotional status, psychosocial functioning, and general quality of life are assessed. These measures also serve as secondary outcomes for the trial. Fifth, a number of measures such as mood, stress, and craving are collected frequently during active treatment to monitor within-treatment changes. Sixth, treatment process measures, assessing therapeutic alliance, processes of change, and client satisfaction are also collected.

Based on these considerations, the final assessment battery assesses the following broad domains: 1) screening and inclusion/exclusion criteria, 2) history/physical, physiologic and laboratory assessments, 3) treatment related expectancies, 4) drinking-related, psychological, and behavioral outcomes, predictors, mediators and generalizability measures, and 5) therapy and medication adherence and therapy process measures. Subject compliance is registered by using attendance records to monitor behavioral intervention participation and a combination of pill counts from returned medication cards plus self-reported medication compliance, using the time-line follow-back procedure.

Schedule of Assessments

Most measures are administered at baseline and again at one or more follow-up points. Measures thought to be particularly sensitive to subject reactivity (e.g., drinking self-report measures) are conducted earlier in the baseline assessment sequence to minimize subsequent assessment reactivity. The primary follow-up assessments take place at postrandomization weeks 8, 16, 26, 52, and 68. Within-treatment measures of drinking and craving are administered at weekly intervals or at each of the MM visits.

A number of sources of information are involved in these assessments. Self-reports, completed by the participants as either paper-and-pencil or computer-assisted forms, represent the largest number of measures. Medical personnel, including participants' MM clinicians, complete others. Others are structured or semistructured interviews conducted by research assistants. All personnel involved in the baseline assessment are blind to the participants' treatment conditions and continue to be blind to their medication condition throughout the trial.

Table 2 presents the list of measures included in the final battery, the constructs that they are thought to measure, who administers them, and the time points at which they are administered.

Table 2. COMBINE Main Trial—Assessment Grid (Major Follow-Up Time Points)

Table 2. COMBINE Main Trial – Assessment Grid (major follow-up time points)

A. Screening Assessments (Prior to Baseline)

	Assessment & Source	Construct/ Purpose	Adm.[5]	Time Estimate (minutes)
	COMBINE Quick Screen with AUDIT (Bohn et al., 1995),	Inclusion/ exclusion criteria	RA	10
	Determinants of participation	Reasons for study participation	SA	1

B. History / Physical, Physiologic and Laboratory Assessments

(*Includes questions for contraindicated Rxs, excluded OTCs & "natural" agents)*

	Assessment & Source	Construct/ Purpose	Adm.[5]	Time Estimate (minutes)	BL	Wk 8	Wk 16	Wk 26	Wk 52	Wk 68
a. History/Physical, Physiologic Assessments										
1.	Demographics		SA	3	√					
2.	History and Physical exam	Health screen	MM	15	√		√			
3.	Psychiatric History		MM	5	√					
4.	Blood pressure[1]	WD measure	MM	3	√	√	√	√	√	√
5.	Heart rate[1]	WD measure	MM	1	√	√	√	√	√	√
6.	Weight & Height	Body mass	MM	2	√	√	√	√	√	√
7.	CIWA-Ar -- Clinical Institute Withdrawal Assessment for Alcohol - Revised (Sullivan et al., 1989)	WD measure	MM	5	√					
b. Laboratory Measurements										
8.	Electrolytes, BUN & Glucose		lab		√	√	√			
9.	CBC		lab		√		√			
10.	Liver Function Tests[2] (AST, GGT, Bilirubin Total & Direct)	*prn* if elevated GGT	lab		√	√	√	√	√	
11.	beta-HCG		lab		√	Repeated if menses are 10 days overdue				
12.	Urinalysis	Health screen	MM		√		√			
13.	Electrocardiogram	Safety	lab		Perform only if clinically indicated					
14.	Breath Alcohol Concentration (breathalyzer)[1]		RA	2	√	√	√	√	√	√
15.	Urine toxicology screen		RA	5	√					
16.	beta-naltrexol levels		lab			Wks 4 & 12				
17.	Acamprosate levels		lab			Wks 4 & 12				
18.	Carbohydrate Deficient Transferrin		lab		√	√	√			
c. Adverse Events										
19.	SAFTEE short form (Levine & Schooler 1986; Jacobson et al., 1989) Side Effects Checklist[1]	Toxicity	MM	7	√	√	√			
20.	Menstrual Calendar[1]	Safety	MM		√	√	√			
21.	Concurrent Medication[1]		MM	3	√	√	√	√	√	√
22.	SAE-Serious Adverse Event Form	Safety	PI/PC		Obtained as indicated clinically					
23.	Inactive Status Form	Reasons for Discontinuation	MM/ PC		Obtained as necessary					

C. Treatment Related Expectancies

	Assessment & Source	Construct/ Purpose	Adm.[5]	Time Estimate (minutes)	BL	Wk 8	Wk 16	Wk 26	Wk 52	Wk 68
1.	Treatment Experiences and Expectancies Questionnaire (Donovan D., unpublished)	Expectancies concerning treatment effectiveness	SA	3	√					

DATA ANALYSIS

Primary (Explanatory) Analyses

COMBINE tests seven primary efficacy hypotheses. These include the traditional ANOVA main effects and interaction tests, based on the 8-cell $2 \times 2 \times 2$ complete factorial design. The three main effect hypotheses test whether there is a mean difference (1) between naltrexone versus placebo, (2) between acamprosate and placebo and (3) between intensive versus brief psychosocial intervention. The three two-way interaction hypotheses test whether the effects of pairs of interventions are additive, i.e., (4) naltrexone plus intensive psychosocial intervention versus naltrexone plus brief psychosocial

Table 2. *(continued)*

D. Assessments of Behavioral Outcomes, Predictors, Mediators & Generalizability

	Assessment & Source	Construct/ Purpose	Adm.[5]	Time Estimate (minutes)	BL	Wk 8	Wk 16	Wk 26	Wk 52	Wk 68
a. Alcohol Consumption										
1.	Time-line Follow-Back Procedure (Sobell & Sobell, 1995)[3]	Primary within-measure of daily alcohol use and patterns	RA	15		√	√			
2.	Form 90-AIR/ED[3] Form 90-F/ED[3] Form 90-A (Miller, 1996)	Primary outcome; comprehensive, daily alcohol use, patterns & Tx; cost-effectiveness data	RA	25	√	√	√	√	√	√
3.	Form 90 AQ	Essential outcome data	RA		Completed if participant is unwilling/unable to complete the full Form-90					
b. Alcohol & Drug Involvement										
4.	Drinker Inventory of Consequences (Miller et al., 1995)	Consequences of drinking since last interview that DRF was administered	SA	7	√	√	√	√	√	√
5	Alcohol Dependence Scale (Skinner & Allen, 1982)	Alcohol Dependence	SA	7	√					
6	SCID-IV Module E (Spitzer, et al., 1992)	Alcohol and Drug abuse & dependence	RA	10	√		√		√	√
7	SCID Modules Form	Summary of Axis I modules completed	RA		√					
8	Drug Use Index (Clayton & Voss, 1981)	Scoring algorithm, yields a global drug use score	(na)	Derived from other measures						
9	ASI Family History Chart (McLellan et al., 1992)	Predictor Mediator	RA	5	√					
10	Alcohol Abstinence Self Efficacy (DiClemente et al., 1994)	Self-efficacy & temptation Prognostic Mediator	SA	8	√		√	√		
11	Composite Outcome Index (Cisler & Zweben, 1999)	Composite measure of drinking and negative consequences	(na)	Derived from other measures						
c. Motivation										
1	Short Form Readiness to Change (alcohol; DiClemente, 1994)	Stage of change Prognostic Mediator	SA	10	√					
d. Craving										
1	Obsessive-Compulsive Drinking Scale[1] (Anton et al., 1995, 1996)	Mediator	SA	6	√	√	√	√		
2	Relapse questions[1] (Weiss et al. , 1997)		SA	1	√	√	√	√		
e. Psychological/Psychiatric Assessments										
1.	SCID Screen Patient Questionnaire (formerly Mini-SCID for DSM-IV (First, et al., 1995)	Screen for various Axis I disorders.	RA	20	√					
2.	SCID Modules Form	Summary of Axis I modules completed	RA		√					
3.	Brief Symptom Inventory (Derogatis 1993) adapted from SCL-90	Symptoms of anxiety, depression, etc.	SA	8	√	√	√	√	√	√
4.	Profile of Mood States[1] (McNair et al., 1981)	Serial measure of mood & treatment response	SA	7	√	√	√			
5.	Perceived Stress Scale[1] (Cohen, et al., 1983) 4-item scale	Serial measure of stress	SA	4	√	√	√		√	

intervention, (5) acamprosate plus intensive psychosocial intervention versus acamprosate plus brief psychosocial intervention, and (6) combination versus mono-pharmacotherapy. The three-way interaction hypothesis (7) tests whether the simultaneous effect of all three interventions (combination pharmacotherapy plus intensive behavioral therapy) differs from that which would be predicted by the main effects and interactions.

Statistical Methods for Primary Analyses

The primary end-of-treatment analyses will evaluate outcomes for the sixteen-week period following randomization. Primary analyses will include all randomized participants, based on the principle of intention-to-treat. Two coprimary endpoints were selected for the evaluation of efficacy: percent days abstinent (PDA) per month

Table 2. *(continued)*

D. Assessments of Behavioral Outcomes, Predictors, Mediators & Generalizability

	Assessment & Source	Construct/ Purpose	Adm.[5]	Time Estimate (minutes)	BL	Wk 8	Wk 16	Wk 26	Wk 52	Wk 68
f. Social Support										
1.	Important People Instrument – revised (Longabaugh et al., 1998)	Measures support for drinking vs. abstinence in patient's social network & importance of network.	RA	12	√		√	√		
g. Quality of Life										
1	GAF Global Assessment of Functioning (First, 1998)	Clinical rating of global functioning used in Axis V of DSM-IV; Outcome	(na)	Derived from other measures						
2	Quality of Life Assessment (Szabo, 1996)	Life functioning & satisfaction with physical & mental health; Health status & outcome	SA	8	√			√	√	
3	SF-12 (Ware & Sherbourne, 1992)	Quality of Life short form	SA	2	√		√		√	
h. Therapy Compliance and Process Measures										
1	Pill Count Form[1]		RA		√	√	√			
2	Medication Noncompliance Checklist[1]	Reasons for med nonadherence	MM		√	√	√			
3	Session Record Forms[1]	Quality control	MM/CBI		√	√	√			
4	Inactive Status Form	Reasons for discontinuing treatment	SA or RA	as indicated clinically						
5	Working Alliance Inventory–Bond subscale[4] (Horvath & Greenberg, 1989)	Perceived therapeutic alliance	SA							
6	Processes of Change Questionnaire (Prochaska et al., 1992)	Processes of change Prognostic mediator	SA	8			√	√		
7	Evaluation Of and Satisfaction With Treatment (Donovan et al., in press)	Client satisfaction and perceived helpfulness of treatment components	SA	10			√			
	Subtotal (minutes):				223	111	154	94	75	61
	Total (hours) for assessments: *including 1 hour for labs, consent and logistical down time				**4.7* hours**	**1.9 hours**	**2.5 hours**	**1.6 hours**	**1.3 hours**	**1.0 hours**

[1] Measures completed at weeks 0, 1, 2, 4, 6, 8, 10, 12 and 16 in addition to other times noted in table.
[2] Liver function tests completed at weeks 4, 8, 12 in addition to other times noted in table.
[3] The Timeline Follow-back procedure is completed at week 0, 1, 2, 4, 6, 8, 10, 12 and 16; the Form-90 is administered at BL and weeks 26, 52 and 68; also administered during treatment phase if time between visits ≥ 6 weeks.
[4] Working Alliance completed after the 3rd MM contact and 3rd CBI session.
[5] CODES for administration: RA (research assistant); SA (self-administered); MM (physician or nurse practitioner); CBI (psychotherapist); PI (Principal Investigator); PC (Project Coordinator); na (not administered, i.e. calculated)

during the treatment period, and time to relapse to heavy drinking (5 or more drinks per day for males, 4 or more for females). A mixed-effect general linear model will be used to evaluate the primary hypotheses, making maximal use of available data. The three treatments will be fixed effects. Standard ANOVA main effects and interactions will be fit, as defined above. The main effect of clinical center will be included as a fixed effect. Time (month since randomization) will be treated as a random effect. A baseline measure of PDA will be computed using the 30 days prior to the participant's last drink; this will be used as a covariate in the model. Time to relapse to heavy drinking will be analyzed using proportional hazards models. Standard ANOVA main effect and interaction parameters will be fit, as defined above. The main effect of clinical center will be included. Participants who are lost to follow-up will be assumed to have relapsed to heavy drinking on the day after their last study contact.

Type I error control. The traditional ANOVA approach of family-wise error control will be used (testing each main effect and interaction at a two-tailed alpha = 0.05 level). A Bonferroni correction will be used to adjust for the two coprimary endpoints. Thus each primary hypothesis will be evaluated at a two-tailed 0.025 level (0.05/2).

Sample Size and Power

To estimate study power, it is necessary to specify the alternative hypothesis. In a two-group design, this essentially means specifying the size of the difference in treatment effect between the two treatment groups. In this factorial design, it means specifying a pattern for the eight cell means. First, we assumed a no interaction model. In that model, power to detect a main effect of 10% is greater than 0.90 for each coprimary endpoint (after adjustment for multiple endpoints). As is always the case in factorial designs, power to detect interactions is much lower, typically less than 0.50. In designing the trial, the Steering Committee had extended discussion of the relative importance of providing definitive evaluations of the main effects of the treatments (e.g., the efficacy of naltrexone, ignoring acamprosate and type of psychotherapy), versus evaluating interaction effects (i.e., the relative efficacy of various combinations of therapies). The only way to have ample power for interactions, would have been to use an incomplete factorial design that would have made (untestable) assumptions about main effects. Ultimately, the SC decided it was preferable to ensure sensitive, reliable assessments of the main effects, settling for modest power for interactions.

Secondary Analyses

In addition to the primary analyses, two sets of secondary analyses are felt to be fundamental to interpreting the main outcome of the trial. These are described below

Secondary Analyses of Post-Treatment Outcomes. While treatment effects during the sixteen-week active treatment period have been selected as the primary measure of treatment efficacy, post-treatment outcomes at weeks 26, 52, and 68 are key secondary analyses that will also be reported in the primary results paper. The primary analyses of the post-treatment outcome will use the same general statistical methodology as the analysis of the in-treatment outcomes. The analyses of PDA and time to first heavy drinking day use cumulative outcome data, from randomization forward. Numerous secondary analyses are anticipated, some of which will evaluate outcomes within specific follow-up periods (e.g., end of treatment to 1 year post-treatment).

Secondary Analyses of Placebo Effects. The inclusion of cell 9 (CBI with no pills or Medical Management) allows an evaluation of the magnitude (and direction) of placebo effects on CBI. This comparison is of interest to psychotherapy practitioners with concerns about medications either enhancing or detracting from behavioral treatment benefits (e.g., attributional negative placebo effects).

Other Preplanned Secondary Analyses. These will include examination of distributional characteristics of primary dependent measures, psychometric analyses of baseline measures, examination of site specific effects, examination of alternative outcome measures (e.g., the Medical Outcomes Study Short Form-12 – Volk et al., 1997; Ware and Sherbourne 1992; the World Health Organization (WHO) Quality of Life instrument – First, 1998; Szabo, 1996; the DSM-IV Global Assessment of Functioning – American Psychiatric Association, 1994), examination of treatment integrity, analysis of outcomes using secondary outcome variables and nonmanipulated variables (such as such as Twelve Step Participation), studies of prognostic indicators, and causal chain analyses (Longabaugh and Wirtz, 2001).

Interim Analyses

A Data and Safety Monitoring Board reviews the accumulating data at regular intervals. Interim analyses of efficacy will be performed 18, 24, and 30 months after the first participant is randomized. Analyses of safety parameters will be performed every 6 months. The details of the approach to monitoring efficacy and safety have been presented (Johnson, 2000) and will be the topic of a forthcoming publication.

QUALITY ASSURANCE

Treatment Delivery Monitoring

A number of procedures are being employed to ensure and document fidelity of the study treatments. These include: 1) preparation of manuals for both MM and CBI approaches, 2) standardization of the selection, training, and certification procedures for MM practitioners and CBI therapists, and 3) establishment of trial-wide procedures for ongoing monitoring of practitioners'/therapists' performance. Thus, CBI therapists must demonstrate competence in different treatment modules (e.g., motivational interviewing) while MM practitioners must evidence skill in handling issues such as nonadherence to the study medication. In addition, checklists have been developed for observing therapists'/practitioners' adherence to the treatment manuals. Those individuals who do not meet performance standards (i.e., fall below criterion ratings on adherence forms) are "red-lined" or decertified and are then required to undergo additional training/supervision to be re-certified so that they can take on new cases. A centralized training center (University of New Mexico) is responsible for trial-wide training, certification, and monitoring of MM practitioners and CBI therapists. On-site supervision of practitioners/therapists is also provided for purposes of facilitating subject compliance, handling case management issues (e.g., clinical deterioration), and monitoring adherence to the study protocol. The inter-rater reliability of therapist ratings for CBI and MM is conducted for 5% of sessions, which are randomly selected.

Data Collection Monitoring. A variety of standard strategies are employed to maximize the quality of data collection. In addition to the protocol, a detailed manual of operations has been developed, containing instructions for performing each procedure and item-specific instructions where required. Centralized training sessions are being

held, explaining study procedures and data collection instruments. The training center also is responsible for centralized certification of staff in the collection of the primary endpoint (drinking) data. Whenever practical, self-report and interview data are collected using electronic data capture, rather than paper forms. This eliminates the data transcription (entry) step, and its associated errors. It also allows validation of data values in real-time, while the participant is available to confirm or correct the recorded value. On an ongoing basis, a sample of paper forms will be sent to the Coordinating Center for re-entry and comparison to the drinking data values entered at the clinical centers (Blumenstein, 1993; Neaton et al., 1990). The monthly study status report contains a variety of tabulations of data completeness, timeliness, and quality.

ORGANIZATION, ADMINISTRATION, AND OVERSIGHT

The principal decision-making body of COMBINE is the *Steering Committee* (SC). The SC oversees all aspects of the design, execution, and publication of the study and is composed of the Principal Investigator of each Clinical Research Unit and the Coordinating Center, and the NIAAA Staff Collaborator. Each has one vote when a vote of the SC is necessary to make a decision. The Steering Committee has designated subcommittees to develop and monitor aspects of the study, reporting recommendations to the SC for approval.

The *Operations Committee* manages the day-to-day operations of the study between SC meetings. It develops the agendas and prepares recommendations for SC meetings, and monitors interim progress of subcommittee tasks and participant recruitment. It meets no less than every other week by telephone and is composed of the Steering Committee chair, subcommittee chairs, NIAAA, and Coordinating Center representatives. Several *specialized subcommittees* function between SC meetings to carry out technical tasks designated by the SC, and report to the Operations Committee.

The *Data and Safety Monitoring Board* (DSMB) is an independent group with expertise in alcoholism treatment, medicine, pharmacology, biostatistics, and bioethics appointed by NIAAA. Its primary role is to advise NIAAA on scientific, safety, ethical, and other policy issues relating to the study. As appropriate, it makes recommendations to the Institute concerning changes in study conduct.

PILOT STUDIES

During protocol development, the Steering Committee identified two pilot studies that were thought to be important "proof of concept" studies prior to initiating the trial. Pilot #1 was an inpatient study of various dose combinations of the two drugs, intended to identify serious toxicities or adherence problems with the combination therapies. Pilot #2 was an outpatient study, using the trial protocol to evaluate the feasibility of the planned procedures and treatments.

Pilot No. 1

A phase II-type dose tolerance study was needed to characterize the independent and combined doses of the medications. Potentially, the increased adverse effects to the independent high medication dose of naltrexone (100 mg) or acamprosate (3 g) could jeopardize medication adherence. While the scientific premise of enhanced efficacy with the combination rests on the summation of neurochemical action at different therapeutic sites (Wild and Reid, 1990; Wise and Bozarth, 1987), there also was potential for aggregation of the same type of adverse effects, which could independently be associated with either medication. For example, headaches are common with both medications (Johnson and Ait-Daoud, 2000a; Johnson and Ait-Daoud, 2000b) and may be markedly more frequent with the combination. Even if the side-effects did not summate directly with the medication combination, it was possible that the numerical increase in symptoms also would prevent use of the combination (Swift et al., 1994). Both medications are associated with different gastrointestinal adverse effects (Johnson and Ait-Daoud, 2000a; Johnson and Ait-Daoud, 2000b) e.g., nausea and abdominal cramping with naltrexone, and diarrhea with acamprosate. While each may produce only mild symptoms, in combination, the collective side effect cluster may exceed what the patient is willing to bear (Swift et al., 1994). If adherence to the combination was poor, the main trial's integrity could be jeopardized by differentially high dropout rates in those study cells. Results from this 4-site pilot (COMBINE Study Research Group, 2003) will inform the main trial on side effect profiles, potential compliance issues, and optimal dosing regimen.

Pilot No. 2

In a feasibility and safety study, the eligibility determinations, interventions, assessments, and all other procedures planned for the trial were performed at all eleven clinical centers. A secondary objective was to provide the staff at each clinical center with experience in all trial procedures and help refine those procedures. The design of this pilot study was identical to that of the main trial with the exception of post-treatment follow-up visits. All randomized participants received four months of therapy. Sites randomized 96 subjects, oversampling three cells in particular: cells 4 and 8, which combined both active pharmacotherapies (to more thoroughly test the tolerability and safety of the combined medications) and cell 9, CBI without medication, to test whether it would be feasible to recruit for a no-pill condition within a pharmacotherapy trial (Johnson BA, et al., 2003).

SIGNIFICANCE AND POTENTIAL CONTRIBUTIONS

With a growing armamentarium of pharmacologic and behavioral treatments for alcohol dependence, studies are needed that extend the knowledge base beyond the basic safety and efficacy yield of single agent placebo-controlled trials to more complex questions regarding combination effects and interactions of pharmacologic agents with psychosocial treatments. The two pilot studies by the COMBINE Research Group indicate that it is feasible to conduct such a combination trial. The objectives of the COMBINE main trial include determining whether the efficacy of combined pharmacotherapy treatment exceeds that of monotherapy, whether pharmacotherapy with a primary care model behavioral intervention is sufficient, whether pharmacotherapy effects exceed those of behavioral therapy, and whether intensive, specialty behavioral therapy adds to the efficacy of pharmacotherapy. In addition to these primary analysis questions, exploratory analyses will examine the mechanisms by which the agents and behavioral interventions mediate their effects, e.g., whether the treatments are additive, synergistic, or even antagonistic. Also, results may indicate whether particular agents and behavioral interventions are better suited to patient subtypes. Finally, two integrated substudies will examine the costs associated with single versus combination treatments and whether genetic subtyping may explain some portion of the variance in response rates. COMBINE's approach to independent and combination testing of effective medications with differentially intensive behavioral interventions offers a new level of design complexity. Findings from this study have the potential to introduce a new era of multimodal alcoholism treatment. [[Cohen et al., 1983; Prochaska et al., 1992; Cisler and Zweben, 1999; First et al., 1996; Levine and Schooler, 1986; Donovan et al., 2002; Spitzer et al., 1992; DiClemente et al., 1994; McLellan et al., 1992; Miller, 1996; McNair et al., 1981; Jacobson et al., 1986; Horvath and Greenberg, 1989; Bohn et al., 1995; Sullivan et al., 1989; DiClemente and Prochaska, 1998; Skinner and Alle, 1982; Mason et al., 2002; Cohen and Williamson, 1988; Anton et al., 1995; Sobell and Sobell, 1995; Derogatis, 1993; Clayton and Voss, 1981; Weiss et al., 1997; Anton et al., 1996]]

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