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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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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

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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

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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

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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

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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.

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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

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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

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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).

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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

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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).

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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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Medication Packaging

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REFERENCES

American Psychiatric Association (1994) *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. DSM-IV. American Psychiatric Association, Washington, DC.

Anton RF, Moak DH, Latham P (1995) The Obsessive Compulsive Drinking Scale: A self rated instrument for the quantification of thoughts about alcohol and drinking behavior. Alcohol Clin Exp Res 19:92–99.

Anton RF, Moak DH, Latham PK (1996) The Obsessive Compulsive Drinking Scale (OCDS): A new method of assessing outcome in alcoholism treatment studies. Arch Gen Psychiatry 53:225–231.

Anton RF, Moak DH, Waid LR, Latham PK, Malcolm RJ, Dias JK (1999) Naltrexone and cognitive behavioral therapy for the treatment of outpatient alcoholics. Am J Psychol 156:1758–1764.

Anton RF, Dominick S, Bigelow M, Westby C (2001a) Comparison of Bio-Rad %CDT TIA and CDTect as laboratory markers of heavy alcohol use and their relationship with γ-glutamyltransferase. Clin Chem 47:1769–1775.

Anton RF, Moak DH, Latham PK, Waid LR, Malcolm RJ, Dias JK, Roberts JS (2001b) Posttreatment results of combining naltrexone with cognitive-behavior therapy for the treatment of outpatient alcoholics. J Clin Psychopharmacol 21:72–77.

Azrin NH, Sisson RW, Meyers R, Godley M (1982) Alcoholism treatment by disulfiram and community reinforcement therapy. J Behav Ther Exper Psychiatry 13:105–112.

Barlow DH, Gorman JM, Shear MK, Woods SW (2000) Cognitive-behavioral therapy, imipramine, or their combination for panic disorder: A randomized controlled trial. JAMA 283:2529–2536.

Barrett D, Morse P (1998) Handling noncompliance, in *Strategies for Facilitating Compliance in Alcoholism Treatment Research* (Zweben A, Barrett D, Carty K, McRee B, Morse P, Rice C, eds), Project MATCH Monograph Series, Volume 7, pp 33–63. NIAAA, US Department of Health and Human Services, NIH Publication No. 98–4144.

Benjamin D, Grant E, Pohorecky LA (1993) Naltrexone reverses ethanol-induced dopamine release in the nucleus accumbens in awake, freely moving rats. Brain Res 621:137–140.

Blumenstein BA (1993) Verifying keyed medical research data. Stat Med 12:1535–1542.

Bohn MJ, Babor TF, Kranzler HR (1995) The Alcohol Use Disorders Identification Test (AUDIT): Validation of a screening instrument for use in medical settings. J Stud Alcohol 56:423–431.

Carty K, Rice C, Barrett D (1998) Strategies for maintaining compliance, in *Strategies for Facilitating Compliance in Alcoholism Treatment Research* (Zweben A, Barrett D, Carty K, McRee B, Morse P, Rice C, eds). Project MATCH Monograph Series, Volume 7, pp 9–32. NIAAA, US. Department of Health and Human Services. NIH Publication No. 98–4144.

Chick J, Erickson CK (1996) Conference summary: Consensus Conference on Alcohol Dependence and the Role of Pharmacotherapy in its Treatment. Alcohol Clin Exp Res 20:391–402.

Chick J, Anton R, Checinski K, Croop R, Drummond DC, Farmer R, Labriola D, Marshall J, Moncrieff J, Morgan MY, Peters T, Ritson B (2000a) A multicentre, randomized, double-blind, placebo-controlled trial of naltrexone in the treatment of alcohol dependence or abuse. Alcohol Alcohol 35:587–593.

Chick J, Howlett H, Morgan MY, Ritson B (2000b) United Kingdom Multicentre Acamprosate Study (UKMAS): a 6-month prospective study of acamprosate versus placebo in preventing relapse after withdrawal from alcohol. Alcohol Alcohol 35:176–187.

Cisler RA, Zweben A (1999) Development of a composite measure for assessing alcohol treatment outcome: Operationalization and validation. Alcohol Clin Exp Res 23:263–271.

Clayton R, Voss H (1981) *Young Men and Drugs in Manhattan: A Causal Analysis*. Washington, DC: US Government Printing Office. National Institute on Drug Abuse Research Monograph No. 39.

Cohen S, Kamarck T, Mermelstein R (1983) A global measure of perceived stress. J Health Soc Behav 24:385–396.

Cohen S, Williamson GM (1988) Perceived stress in a probability sample of the United States, in (Spacapan S, Oskamp S eds), *The Social Psychology of Health*, pp 31–67. Sage, Newbury Park, CA.

COMBINE Study Research Group (2003) Testing Combined Pharmacotherapies and Behavioral Interventions for Alcohol Dependence (The COMBINE Study): A Pilot Feasibility Study. Alcohol Clin Res Exp 27:1123–1131.

Connors GJ, Allen JP, Cooney NL, DiClemente CC, Tonigan JS, Anton RF (1994) Assessment issues and strategies in alcoholism treatment matching research. J Stud Alcohol Suppl 12:92–100.

Davidson D, Palfai T, Bird C, Swift R (1999) Effects of naltrexone on alcohol self-administration in heavy drinkers. Alcohol Clin Exp Res 23:195–203.

Derogatis LR (1993) *BSI. Brief Symptom Inventory. Administration, Scoring, and Procedures Manual*. 3rd ed. National Computer Systems, Inc., Minneapolis, MN.

Diana M, Pistis M, Muntoni A, Gessa G (1996) Mesolimbic dopaminergic reduction outlasts ethanol withdrawal syndrome: evidence of protracted abstinence. Neuroscience 71:411–415.

DiClemente CC, Carbonari JP, Montgomery RPG, Hughes SO (1994) Alcohol abstinence self-efficacy scale. J Stud Alcohol 55:141–148.

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DiClemente CC, Prochaska JO (1998) Toward a comprehensive, transtheoretical model of change: Stages of Change and Addictive Behaviors, in *Treating Addictive Behaviors* (Miller WR, Heather N eds), pp 3–24. 2nd ed. Plenum, New York.

Donovan DM, Kadden RM, DiClemente CC, Carroll KM (2002) Client satisfaction with three therapies in the treatment of alcohol dependence: Results from Project MATCH. Am J Addict 11:291–304.

Emrick CD, Tonigan JS, Montgomery H, Little L (1993) Alcoholics Anonymous: What is currently known? In *Research on Alcoholics Anonymous: Opportunities and Alternatives* (McCrady BS, Miller WR eds), pp 41–76. Rutgers Center of Alcohol Studies, New Brunswick, NJ.

First MB, Gibbon M, Williams JBW, Spitzer RL (1996) *Mini-SCID: Computer Administered DSM-III-R Screened Based on the Structured Clinical Interview for DSM-III-R. User's Manual*. Multi-Health Systems, Inc., and American Psychiatric Association, Washington, D.C..

First MB (1998) *GAF Report for the Global Assessment of Functioning Scale*. Multi-Health Systems, North Tonawanda, NY.

Foster Olive M, Nannini MA, Ou CJ, Koenig HN, Hodge CW (2002) Effects of acute acamprosate and homotaurine on ethanol intake and ethanol-stimulated mesolimbic dopamine release. Eur J Pharmacol 437: 55–61.

Froelich JC, Harts J, Lumeng L, Li TK (1990) Naloxone attenuates voluntary ethanol intake in rats selectively bred for high ethanol preference. Pharmacol Biochem Behav 35:385–390.

Garbutt JC, West SL, Carey TS, Lohr KN, Crews FT (1999) Pharmacological treatment of alcohol dependence: a review of the evidence. JAMA 281:1318–1325.

Garnick D, Hendricks AM, Dulski JD, Thorpe KE, Horgan C (1994) Characteristics of private-sector managed care for mental health substance abuse treatment. Hosp Community Psychiatry 45:1201–1205.

George SR, Roldan L, Lui A, Naranjo CA (1991) Endogenous opioids are involved in genetically determined high preference for alcohol consumption. Alcohol Clin Exp Res 15:668–672.

Gessa GL, Montoni F, Collu M, Vargiu L, Mereu G (1985) Low doses of ethanol activate dopaminergic neurones in the ventral tegmental area. Brain Res 348:201–203.

Heinala P, Alho H, Kiianmaa K, Lonnqvist J, Kuoppasalmi K, Sinclair JD (2001) Targeted use of naltrexone without prior detoxification in the treatment of alcohol dependence: a factorial double-blind, placebo-controlled trial. J Clin Psychopharmacol 21:287–292.

Hemby SE, Johnson BA, Dworkin SI (1997) Neurobiological basis of drug reinforcement, in *Drug Addiction and its Treatment: Nexus of Neuroscience and Behavior* (Johnson B, Roache J, eds). Lippincott-Raven, Philadelphia.

Heyser CJ, Schulteis G, Durbin P, Koob GF (1998) Chronic acamprosate eliminates the alcohol deprivation effect while having limited effect on baseline responding for ethanol in rats. Neuropsychopharmacology 18: 125–133.

Horvath AO, Greenberg LS (1989) Development and validation of the Working Alliance Inventory. J Counseling Psychol 36:223–233.

Howard KI, Kopta SM, Krause MS, Orlinsky DE (1986) The dose-effect relationship in psychotherapy. Am Psychol 41:159–164.

Jacobson AF, Goldstein BJ, Dominguez RA, Steinbook RM (1986) Interrater agreement and intraclass reliability measures of SAFTEE in psychopharmacologic clinical trials. Psychopharmacol Bull 22:382–388.

Johnson BA (2000) "A multi-center study of the toxicity and tolerance of naltrexone and acamprosate alone and in combination" Presented during the Design and rational for COMBINE, a multi-site study on combining medications and behavioral interventions for alcohol dependence at the Research Society on Alcoholism Annual Scientific Meeting in Denver, Colorado.

Johnson BA, Ait-Daoud N (2000a) Neuropharmacological treatments for alcoholism: Scientific basis and clinical implications. Psychopharmacology 149:327–344.

Johnson BA, Ait-Daoud N (2000b) Medications to treat alcoholism. Alcohol Res Health 23:99–106.

Johnson BA, O'Malley SS, Ciraulo SA, Roache JD, Chambers RA, Sarid-Segal O, Couper D (2003) Dose-ranging kinetics and safety assessment of naltrexone and acamprosate both alone and combined in alcohol-dependent subjects. J Clin Psychopharmacol, in press.

Kadden RP, Carroll K, Donovan D, Cooney N, Monti P, Abrams D, Litt M, Hester R (1995) *Cognitive-Behavioral Coping Skills Therapy Manual: A Clinical Research Guide for Therapists Treating Individuals with Alcohol Abuse and Dependence. Project MATCH Monograph series, Vol. 3*, National Institute on Alcohol Abuse and Alcoholism, Bethesda, MD.

Koob GF (1992) Drugs of abuse: anatomy, pharmacology and function of reward pathways. Trends Pharmacol Sci 13:177–184.

Kornet M, Goosen C, Van Ree JM (1991) Effect of naltrexone on alcohol consumption during chronic alcohol drinking and after a period of imposed abstinence in free-choice drinking rhesus monkeys. Psychopharmacologia 104(3):367–376.

Kranzler HR (2000a) Medications for alcohol dependence- new vistas. JAMA 284:1016–1017.

Kranzler HR, Modesto-Lowe V, Van Kirk J (2000b) Naltrexone vs. nefazodone for treatment of alcohol dependence. A placebo-controlled trial. Neuropsychopharmacology 22:493–503.

Kranzler HR, Van Kirk J (2001) Efficacy of Naltrexone and Acamprosate for Alcoholism Treatment: A Meta-Analysis. Alcohol Clin Exp Res 25:1335–1341.

Krystal JH, Cramer JA, Kroll W, Kirk G, Rosenheck RA, Veterans Affairs Naltrexone Cooperative Study 425 Group (2001) Naltrexone in the treatment of alcohol dependence. N Engl J Med 345:1734–1739.

Levine J, Schooler N (1986) SAFTEE: A technique for the systematic assessment of side effects in clinical trials. Psychopharmacol Bull 22: 343–381.

Lhuintre JP, Moore N, Tran G, Steru L, Langrenon S, Daoust M, Parot P, Ladure P, Libert C, Boismare F, Hillemand B (1990) Acamprosate appears to decrease alcohol intake in weaned alcoholics. Alcohol Alcohol 25:613–622.

Litten RZ, Allen JP (1991) Pharmacotherapies for alcoholism: promising agents and clinical issues. Alcohol Clin Exp Res 15:620–633.

Litten RZ, Fertig J (1996) International update: new findings on promising medications. Alcohol Clin Exp Res 20(8 Suppl):216A-218A.

Litten RZ, Allen JP (1998) Advances in development of medications for alcoholism treatment. Psychopharmacology 139:20–33.

Litten RZ, Allen J, Fertig J (1996) Pharmacotherapies for alcohol problems: a review of research with focus on developments since 1991. Alcohol Clin Exp Res 20:859–876.

Littleton J (1995) Acamprosate in alcohol dependence: how does it work? Addiction 90:1179–1188.

Littleton J, Little H (1994) Current concepts of ethanol dependence. Addiction 89:1397–1412.

Longabaugh R, Wirtz PW, Zweben A, Stout RL (1998) Network support for drinking, Alcoholics Anonymous and long term matching effects. Addiction 93:1313–1333.

Longabaugh R, Wirtz PW (eds) (2001) *Project MATCH: Hypotheses, Results, and Causal Chain Analyses. Project MATCH Monograph Series, Volume 8*. National Institute on Alcohol Abuse and Alcoholism, Bethesda, MD.

Mason B (2001) *Acamprosate treatment of alcohol dependence: Results of the US multicenter study*. Presented at Society of Biological Psychiatry, 2001; New Orleans, LA.

Mason BJ, Ownby RL (2000) Acamprosate for the treatment of alcohol dependence: A review of double-blind, placebo-controlled trials. CNS Spectrums 5:58–69.

Mason BJ, Ownby RL (2002) Treatment of alcohol-dependent outpatients with acamprosate: A clinical review. J Clin Psychiatry 62(suppl 20):42–48.

Mason BJ, Goodman AM, Dixon RM, Abdel Hameed MH, Hulot T, Wesnes K, Hunter JA (2002) A pharmacokinetic and pharmacodynamic drug interaction study of acamprosate and naltrexone. Neuropsychopharmacology 27:596–606.

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McCaul ME, Wand GS, Eissenberg T, Rohde CA, Cheskin LJ (2000a) Naltrexone alters subjective and psychomotor responses to alcohol in heavy drinking subjects. Neuropsychopharmacology 22:480–492.

McCaul ME, Wand GS, Rohde C, Lee, SM (2000b) Serum 6-beta-naltrexol levels are related to alcohol responses in heavy drinkers. Alcohol Clin Exp Res 24:1385–1391.

McLellan AT, Kushner H, Metzger M, Peters R, Smith I, Grissom G, Pettinati H, Argeriou M (1992) The fifth edition of the Addiction Severity Index. J Subst Abuse Treatment 9:199–213.

McNair DM, Lorr M, Droppleman LF (1981) *Profile of Mood States*. Educational and Industrial Testing Service, San Diego, CA.

Meyers RJ, Smith JE (1995) *Clinical guide to alcohol treatment: The community reinforcement approach.* Guilford Press, New York.

Miller WR (1996) Form 90: A structured assessment interview for drinking and related behaviors. In M. E. Mattson ME (Ed), *NIAAA Project MATCH Monograph Series, Vol. 5*. U.S. Department of Health and Human Services, Bethesda, MD.

Miller WR, Rollnick S (1991) *Motivational interviewing: Preparing people to change addictive behavior.* Guilford Press, New York.

Miller WR (ed) (2003) *Combined Behavioral Intervention: A Clinical Research Guide for Therapists Treating Individuals with Alcohol Abuse and Dependence, COMBINE Monograph Series (Vol. 1)*. NIH Publication, National Institute on Alcohol Abuse and Alcoholism, Public Health Service, U.S. Department of Health and Human Services, in press.

Miller WR, Zweben A, DiClimente C, Rychtarik R (1994) *Motivational Enhancement Therapy Manual: A Clinical Research Guide for Therapists Treating Individuals with Alcohol Abuse and Dependence. Project MATCH Monograph Series, Vol 2*. National Institute on Alcohol Abuse and Alcoholism, Bethesda, MD.

Monti PM, Rohsenow DJ, Hutchison KE, Swift, RM, Mueller, TI, Colby, SM, Brown, RA, Gulliver, SB, Gordon, A, Abrams, DB (1999) Naltrexone's effect on cue-elicited craving among alcoholics in treatment. Alcohol Clin Exp Res 23:1386–1394.

Monti PM, Monti PM, Rohsenow DJ, Swift RM, Gulliver SB, Colby SM, Mueller TI, Brown RA, Gordon A, Abrams DB, Niaura RS, Asher MK (2001) Naltrexone and cue exposure with coping and communication skills training for alcoholics: treatment process and 1-year outcomes. Alcohol Clin Exp Res 25:1634–1647.

Morris PLP, Hopwood M, Whelan G, Gardiner J, Drummond E (2001) Naltrexone for alcohol dependence: a randomized controlled trial. Addiction 96:1565–1573.

Neaton JD, Duchene AG, Svndsen KH, Wentworth D (1990) An examination of the efficiency of some quality assurance methods commonly employed in clinical trials. Stat Med 9:115–124.

Nowinski J, Baker S, Carroll K (1995) *Twelve Step Facilitation Therapy Manual: A Clinical Research Guide for Therapists Treating Individuals with Alcohol Abuse and Dependence. Project MATCH Monograph Series, Vol. 1*. National Institute on Alcohol Abuse and Alcoholism, 92–1893, Bethesda, MD.

O'Malley SS, Froehlich JC (2003) Advances in the use of naltrexone: An integration of preclinical and clinical findings. Recent Dev Alcohol 16:217–245.

O'Malley SS, Jaffe AJ, Chang G, Schottenfeld RS, Meyer RE, Rounsaville B (1992) Naltrexone and coping skills therapy for alcohol dependence. Arch Gen Psychiatry 49:881–887.

O'Malley SS, Jaffe AJ, Chang G, Rode S, Schottenfeld R, Meyer RE, Rounsaville B (1996) Six-month follow-up of naltrexone and psychotherapy for alcohol dependence. Arch Gen Psychiatry 53:217–224.

Paille FM, Guelfi JD, Perkins AC, Royer RJ, Steru L, Parot P (1995) Double blind randomized multicentre trial of acamprosate in maintaining abstinence from alcohol. Alcohol Alcohol 30:239–247.

Pettinati H, Weiss R, Miller W, Donovan D, Rounsaville B (2000) *Medical Management Treatment Manual Unpublished manual, COMBINE*. National Institute on Alcohol Abuse and Alcoholism, Bethesda, MD.

Popp RL, Lovinger DM (2000) Interaction of acamprosate with ethanol and spermine on NMDA receptors in primary cultured neurons. Eur J Pharmacol 394:221–231.

Prochaska JO, DiClemente CC, Norcross JC (1992) In search of how people change: Applications to addictive behaviors. Am Psychol 47: 1102–1114.

Project MATCH Research Group (1993) Project MATCH: Rationale and Methods for a Multisite Clinical Trial Matching Patients to Alcoholism Treatment. Alcohol Clin Exp Res 17:1130–1145.

Reid LD, Hubbell CL (1987) Excess of drinking related to excess activity of opioid systems. Alcohol 4:149–168.

Roberts JS, Anton RF, Latham PK, Moak DH (1999) Factor structure and predictive validity of the Obsessive Compulsive Drinking Scale. Alcohol Clin Exp Res 23:1484–1491.

Sass H, Soyka M, Mann K, Zieglgansberger W (1996) Relapse prevention by acamprosate. Results from a placebo-controlled study on alcohol dependence. Arch Gen Psychiatry 53:673–680.

Skinner HA, Allen BA (1982) Alcohol dependence syndrome: Measurement and validation. J Abnormal Psychology 91:199–209.

Sobell LC, Sobell MB (1995) *Timeline Followback Computer Software*. Addiction Research Foundation, Toronto.

Spanagel R, Zieglgansberger W (1997) Anti-craving compounds for ethanol: New pharmacological tools to study addictive processes. Trends Pharmacol Sci 18:54–58.

Spitzer RL, Williams JB, Gibbon M, First MB (1992) The Structured Clinical Interview for DSM-III–R (SCID): I. History, rationale, and description. Arch Gen Psychiatry 49:624–629.

Sullivan JT, Sykora K, Schneiderman J, Naranjo CA, Sellers EM (1989) Assessment of alcohol withdrawal: The revised Clinical Institute Withdrawal Assessment for Alcohol scale (CIWA-AR). Br J Addict 84:1353–1357.

Swift RM, Whelihan W, Kuznetsov O, Buongiorno G, Hsuing H (1994) Naltrexone-induced alterations in human ethanol intoxication. Am J Psychiatry 151:1463–1467.

Szabo S (1996) The World Health Organization Quality of Life (WHOQOL) Assessment Instrument, in *Quality of Life and Pharmacoeconomics in Clinical Trials* (Spiker B ed), 2nd ed, pp 355–362. Philadelphia: Lippincott-Raven Publishers.

Tabakoff B, Hoffman PL (1983) Alcohol interactions with brain opiate receptors. Life Sci 32:197–204.

Volk RJ, Cantor SB, Steinbauer JR, Cass AR (1997) Alcohol use disorders, consumption patterns, and health-related quality of life in primary care patients. Alcohol Clin Exp Res 21:899–905.

Volpicelli JR, Davis M, Olgin J (1986) Naltrexone blocks the post-shock increase of alcohol consumption. Life Sci 38:841–847.

Volpicelli JR, Alterman AI, Hayashida M, O'Brien CP (1992) Naltrexone in the treatment of alcohol dependence. Arch Gen Psychiatry 49:876–880.

Volpicelli JR, Watson NT, King AC, Sherman C, O'Brien CP (1995) Effect of naltrexone on alcohol "high" in alcoholics. Am J Psychiatry 152:613–615.

Volpicelli JR, Rhines KC, Rhines JS, Volpicelli LA, Alterman AI, O'Brien CP (1997) Naltrexone and alcohol dependence: Role of subject compliance. Arch Gen Psychiatry 54:737–742.

Ware JE, Sherbourne CD (1992) The MOS 36-Item Short-Form Health Survey (SF-36): I. Conceptual Framework and Item Selection. Med Care 30:473–481.

Weiss RD, Griffin ML, Hufford C, Muenz LR, Najavits LM, Jansson SB, Kogan J, Thompson HJ (1997) Early prediction of initiation of abstinence from cocaine: Use of a craving questionnaire. Am J Addict 6:224–231.

Whitworth AB, Fisher F, Lesch OM, Nimmerrichhter A, Oberbauer H, Platz T, Potgieter WH, Fleischhaker WW (1996) Comparison of acamprosate and placebo in long-term treatment of alcohol dependence. Lancet 347:1438–1442.

Wild KD, Reid LD (1990) Modulation of ethanol intake by morphine: evidence for a central site of action. Life Sci 47:49–54.

Wise RA, Bozarth MA (1987) A psychomotor stimulant theory of addiction. Psych Rev 94:469–492.

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