Choosing Pharmacotherapies for the COMBINE Study—Process and Procedures: An Investigational Approach to Combination Pharmacotherapy for the Treatment of Alcohol Dependence*

ROBERT SWIFT, M.D., PH.D.,1 AND HELEN M. PETTINATI, PH.D.1

Center for Alcohol and Addiction Studies, Department of Psychiatry and Human Behavior, Brown University, Box G-BH, Providence, Rhode Island 02912

ABSTRACT. Objective: This article describes the process by which the COMBINE investigators evaluated and chose the two pharmacotherapies to be studied in COMBINE. Method: The pharmacotherapies were chosen through a consensus process that involved the evaluation of neuropharmacological agents known to modify alcohol consumption or other alcohol-related behaviors in animals and humans. Medications were classified according to the published evidence, with the highest ranking given to those with evidence of efficacy in human clinical trials. The investigators also considered evidence for safety, potential drug-drug interactions, management of side effects, optimal dose, treatment duration, availability of the medication and integration with the psychosocial therapies. The full evaluation required conducting two pilot studies and the development of an instrument to monitor safety, the COMBINE Systematic Assessment for Treatment Emergent Events. Results: Naltrexone, at a dose of 100 mg per day, and acamprosate, at a dose of 3,000 mg per day, were chosen for the study. The medications were administered for a period of 4 months, concurrent with the COMBINE psychosocial therapies Conclusions: The results of the decision making with respect to medications and safety monitoring resulted in a well-planned and well-executed study that minimized risks to the participants. (J. Stud. Alcohol, Supplement No. 15: 141-147, 2005)

COMBINED pharmacotherapy is an accepted strategy for many medical and psychiatric conditions, yet it has only recently been considered for the treatment of alcohol dependence (e.g., National Institute on Alcohol Abuse and Alcoholism [NIAAA] COMBINE Study). Researchers have not attempted many combined pharmacotherapy studies in alcohol-dependent patients because of the inherent complexity of the task. Studying more than one medication in a clinical trial requires (1) more procedures to control more potentially confounding variables and (2) pharmacological sophistication in monitoring and managing medication interactions.

In choosing which medications to combine for study, it is essential to first identify specific neurobiological mechanisms that underlie treatment response. Then compounds that are thought to act through these mechanisms can be identified and tested. At the same time, it is essential to be fully informed about potential adverse events of these medication candidates and medication interactions. Finally, it is important to determine if patient selection will be a factor in responses to medications. There is marked heterogeneity among alcoholics in the drinking patterns, age of onset and associated personality and psychiatric comorbidity. Pharmacogenetics may also explain pharmacological treatment response variability and tolerability. For example, Oslin et al. (2003) reported that patients with one or two copies of the Asp40 variant of the mu-opioid receptor (OPRM1) responded better to naltrexone than those with the Asn40 variant (73.9% vs 49.0%).

Basic safety and efficacy studies are needed for a full and meaningful evaluation of promising medication combinations. Investigations of new medications, especially medication combinations, require human safety and tolerability studies before launching randomized clinical trials. Medication combinations for alcohol-dependent patients must also be tested with yet a third substance, alcohol. Thus, it is paramount to conduct safety studies that uncover interactions between the medications to be investigated as well as substances (e.g., alcohol) likely to be used by patients while in treatment.

The purpose of this article is to provide information on the process and implementation of testing combinations of pharmacotherapies as part of a controlled clinical trial of
patients with alcohol use disorders. We briefly describe the information necessary to select medications to combine for treatment; the preclinical paradigms used to evaluate safety and efficacy of the medications together and also in the presence of alcohol; and the additional trial monitoring required for safety, adherence and efficacy in trials of combined pharmacotherapy.

Background

The COMBINE Study was developed in response to a Request for Applications (RFA) developed by NIAAA. The investigators were charged by the RFA to develop a pharmacological treatment regimen composed of two medications that could be compared to placebo, singly and in combination. The RFA reviewed the current status of pharmacotherapies for alcoholism and listed a number of medications currently used for pharmacotherapy of alcohol dependence or under development.

After 11 clinical sites and a coordinating center were selected through a peer-reviewed process, a Steering Committee composed of the COMBINE investigators met regularly through on-site meetings and conference calls to develop the protocol for the study. It was recognized that the results of COMBINE would be well publicized and highly scrutinized. Therefore, the investigators collectively felt a responsibility to the field to conduct a study of the highest scientific quality, utilizing the best or the most promising research technologies, with findings that should be relevant to researchers, clinicians and patients.

A Pharmacotherapy Committee composed of COMBINE investigators was formed to review potential medication candidates for study and to make recommendations to the Steering Committee about which medications to study, the dosage of medications to use and the timing duration of treatment with each medication. Simultaneously, a Psychosocial Treatment Committee met to consider psychosocial treatments to be integrated with the pharmacotherapies. The two committees kept in frequent communication to facilitate the coordination.

As part of the peer-review process, each of the 11 sites chosen to participate in the COMBINE Study had submitted a grant proposal that included the study of two different medications, in combination. The studies and their medications were reviewed and discussed. The medications proposed in the initial grants included naltrexone, acamprosate, disulfiram and selective serotonin reuptake inhibitors (SSRIs).

There were three main considerations that the Pharmacotherapy Committee evaluated in choosing the medications: evidence for efficacy in the treatment of alcohol dependence, safety and tolerability of the medications in alcohol-dependent humans and medication availability. A secondary consideration included choosing medications that had different neuropharmacological mechanisms of action so that the effects on reducing drinking might be complementary or synergistic. The Pharmacotherapy Committee was also charged with making recommendations about the doses of the medications to be administered, the duration of medication treatment and the dosage form.

Review of potential pharmacotherapies and their scientific basis

At the time the protocol was being developed in 1997, there were many potential medications that were described as reducing alcohol consumption in animals or humans or treating alcohol dependence in published preclinical or clinical studies. As a drug, ethyl alcohol is quite atypical. It has a complex pharmacology, including complexity in its pharmacokinetics and pharmacodynamics. The ethanol molecule is small and possesses both hydrophobic and hydrophilic properties. Although ethanol has no single "receptor," these properties allow it to bind to hydrophobic pockets in many membrane-bound protein molecules, including receptors, ion channels, membrane-bound enzymes and second messenger complexes (Dwyer and Bradley, 2000). The binding of alcohol to diverse membrane proteins results in many physiological and behavioral effects of alcohol. For example, alcohol is simultaneously stimulating and sedating (Martin et al., 1993).

Although the complex neurobiology of alcohol can add to the difficulty in treatment, the multiple actions of ethanol provide many potential targets for the therapeutic pharmacologist. Indeed, the multiple pharmacological actions of ethanol argue that a pharmacotherapy for alcoholism must address multiple pharmacological actions to be maximally effective. Because most medications proposed for the treatment of alcohol dependence affect one neurotransmitter system, it made sense to combine more than one medication to potentially affect multiple neurotransmitter systems.

A primary role of the brain is integration, and the diverse effects of alcohol are integrated into complex behavioral systems that produce and maintain alcohol dependence. Two prominent hypotheses include the (1) Psychomotor Stimulant, Incentive Sensitization Hypothesis and the (2) Drive Reduction, Protracted Withdrawal, Allostasis Hypothesis. The Psychomotor Stimulant, Incentive Sensitization Hypothesis posits that drugs that cause dependence, including alcohol, release dopamine in the nucleus accumbens of the brain. Repeated alcohol use results in a sensitization of the dopamine system, leading to increased salience of alcohol-associated stimuli, drug craving and dependence (Robinson and Berridge, 1993; Wise and Bozarth, 1987). Studies with alcohol-consuming rodents showed that alcohol releases dopamine in the nucleus accumbens and that, over time, dopamine release begins to occur before alcohol consumption, in response to stimuli associated with alco-
hol consumption (Weiss et al., 1993). Brain structures that are capable of inhibiting the nucleus accumbens, such as the orbital prefrontal cortex, gradually become overwhelmed by the sensitized dopamine system or are also directly inhibited by chronic alcohol. The result of these changes results in increasing alcohol consumption over time and eventually a loss of control over drinking.

The Drive Reduction, Protracted Withdrawal, Allostasis Hypothesis posits that repeated alcohol and drug use result in brain adaptive changes over time so that normal brain function requires the constant presence of alcohol. When alcohol is not present, the individual experiences symptoms of protracted withdrawal and anhedonia, and therefore continues to use alcohol to mitigate these unpleasant symptoms (Koob and Le Moal, 2001; Littleton and Little, 1994).

Other brain systems may also play a role in the development and maintenance of alcohol dependence. Alcohol dependence is common in certain anxiety disorders, such as panic disorder, social anxiety disorder and posttraumatic stress disorder, suggesting a relationship between brain structures that mediate anxiety and alcohol. Anxiety is a prominent symptom of alcohol withdrawal, and most medications that are commonly used to treat alcohol withdrawal have anxiolytic properties. Several medications that are proposed as pharmacotherapies for the treatment of alcohol dependence have anxiolytic properties, including buspirone, SSRIs, beta-adrenergic blockers and some antiepileptic medications (e.g., gabapentin).

All of these possible multiple mechanisms of alcohol led NIAAA to seek research applications for study of multiple medications in the RFA that led to the COMBINE Study. Furthermore, in considering which medications to study, the COMBINE Study Research Group was most attracted to the concept of studying different medications with different mechanisms of action.

Criteria for candidate medications

On the basis of the scientific reviews of the neurobiology of alcohol dependence and the preclinical and clinical data available (Garbutt et al., 1999; Litten and Allen, 1998; Swift, 1999), the Pharmacotherapy Committee developed a list of candidate medications and ranked them according to preference. The medications were classified into three hierarchical groups, based on demonstrated efficacy in the treatment of alcohol abuse/dependence, regulatory agency approval, availability of the medication and safety and tolerability in humans.

The first group of medications was considered to be the best candidate medications for the COMBINE Study. Most of these medications had considerable preclinical evidence as well as clinical evidence for efficacy in placebo-controlled clinical trials and had been approved for the treatment of alcohol dependence by the Food and Drug Administration (FDA), or its counterpart in foreign countries. Disulfiram and naltrexone were approved in the United States, and acamprosate, calcium carbimide and tiapride were approved in one or more European countries and/or Australia.

The second group of medications was not specifically approved for the treatment of alcohol dependence by a health regulatory agency; however, there was some evidence for efficacy in human clinical trials of alcohol dependence, and these medications were marketed and available. Medications in this second group were also potential candidates for the COMBINE Study. These included other selective opioid antagonists (nalmefene), serotonin reuptake blockers (e.g., sertraline, fluoxetine, citalopram), buspirone, ondansetron, tricyclic antidepressants (desipramine, imipramine), adrenergic blockers (atenolol), dopamine agonists and antagonists, sedatives (gamma-hydroxybutyrate), antiepileptics (carbamazepine), serotonin-3 receptor antagonists (ondansetron) and serotonin-2 receptor antagonists (ritanserin).

The third group of medications were shown to reduce alcohol consumption in animal models of alcoholism and/or were shown anecdotally to improve alcohol-dependence treatment, but not within controlled clinical studies. Some of these medications, such as calcium channel blockers (verapamil), were in clinical use for the treatment of other conditions, but most of these medications had not been tested formally in human alcoholics and did not have significant evidence for safety in humans. In addition, most of the medications in this third group were not commercially available. The Pharmacotherapy Committee rejected this third group of medications as candidates for COMBINE, given the lack of clinical based evidence for efficacy. It was decided that the chosen medication must have solid evidence of efficacy in the treatment of alcohol dependence in humans; it would be risky and premature to test a medication that was thought to be effective on the basis of animal data and/or early human preclinical data, in a large Phase 3 multisite trial such as COMBINE.

After extensive review of the clinical and behavioral pharmacology of medication candidates, it was decided that the opioid antagonist, naltrexone, and the glutamatergic modulator, acamprosate, were thought to best meet the selection criteria; they were, therefore, chosen for the two medications to be tested in the COMBINE Study. Naltrexone and acamprosate each had been extensively studied in animal models of alcohol dependence and rather consistently reduced alcohol drinking across various models. Naltrexone was shown to reduce alcohol consumption in nonhuman primates and rodents under a variety of conditions and behavioral schedules by reducing the reinforcing effects of alcohol (Sinclair, 1996). Acamprosate was shown to reduce the alcohol deprivation effect, characterized by an increased rebound consumption in animals transiently
deprived of alcohol (Spanagel et al., 1996). Each medication also had been studied in placebo-controlled clinical trials in human alcoholics, and each medication was found in most (but not all) studies to be superior to placebo (Garbutt et al., 1999; Swift, 1999). These two medications also had the advantage of having complementary mechanisms of action in that they acted on different components of alcoholism dependence. Naltrexone is considered to primarily act to reduce craving and positive reinforcement, through its action on opioid and (indirectly) on dopaminergic systems. Acamprosate may reduce protracted alcohol withdrawal through stabilization of glutamatergic N-methyl-D-aspartate receptors that are upregulated and hyperexcitable due to chronic alcohol. It was hoped that the different mechanisms of action of acamprosate and naltrexone would result in additive or synergistic effects on improving drinking outcomes.

Disulfiram, a Group I medication that was available in the United States and FDA approved for the treatment of alcohol dependence, was not chosen primarily because of the paucity of published evidence for its efficacy. Likewise, tiapride and calcium carbimide were not chosen due to less evidence of treatment efficacy; they also were not FDA approved and were not readily available.

The results of a pharmacotherapy study of placebo, acamprosate, naltrexone and the combination independently conducted in Germany (Kiefer et al., 2003) subsequently supported the decision of the COMBINE investigators to study naltrexone and acamprosate. The results of this German study showed efficacy for acamprosate and naltrexone compared with placebo. There was little evidence for an additive effect in that the combination of naltrexone and acamprosate showed reduced drinking compared with placebo and acamprosate alone but not with naltrexone alone. However, this study had a sample size considerably smaller than COMBINE and may have not been adequately powered to show additive treatment effects.

**Possible adverse effects of medication and of combining medications**

Obviously, for the study medications to have any utility, they would have to be well tolerated by patients, with a low incidence of side effects and few if any serious adverse effects. A second consideration of the Pharmacotherapy Committee was, therefore, medication safety and tolerability. Because medication-related adverse events increase exponentially with the number of medications (i.e., taking twice as many medications increases the chance of adverse effects fourfold), combination pharmacotherapy for alcohol dependence was a particular concern. Because there were few published studies of pharmacotherapies for alcoholism studied in combination, the pharmacological and behavioral interactions that might occur with combined medications were unknown. Potential pharmacological interactions might include increased side effects and/or toxicity and alteration in blood levels. Potential behavioral interactions might include one drug reducing an effect such as craving, which was necessary for the action of the second drug.

To monitor adverse effects and medication side effects, a subcommittee of investigators developed a system for eliciting and reporting medication-related adverse events. They adapted a pre-existing side-effect scale, the Systematic Assessment for Treatment Emergent Events (SAFTEE), to the specific medications used in COMBINE (Levine and Schooler, 1986). The process by which the COMBINE SAFTEE scale was developed and implemented is described in detail by Johnson et al. (this supplement).

**Study design considerations**

Study designs that include more than one medication can be highly varied, depending on the rationale for combining medications. The rationale also will guide whether the two medications will be given simultaneously or in sequence. Sequencing medications might occur where a medication is added to (augmenting) another medication when it becomes clear that the efficacy of the initial medication is not as potent in a particular patient as it may be in other patients. Or different medications may be needed to target sequential stages of recovery, each of which may require different treatment mechanisms. Medications may be given simultaneously so as to target different neurobiological mechanisms at the same time, to increase treatment response by adding two pharmacological agents together that produce only modest treatment effects alone or to produce a synergistic effect that cannot be obtained with either pharmacotherapy separately. It would be important, for example, to demonstrate how modest effects from one pharmacotherapy could be enhanced when delivered in the presence of a complementary pharmacotherapy. In COMBINE, our rationale in combining two selected medications, naltrexone and acamprosate, was primarily to target different neurobiological mechanisms at the same time. Naltrexone would potentially target the “Psychomotor Stimulant, Incentive Sensitization” aspects of alcohol dependence, and acamprosate would target the “Drive Reduction, Protracted Withdrawal, Allostasis” aspects. Combined, these medications would potentially increment treatment response (see further explanation below and in Mason, this supplement).

**Determination of treatment duration**

The Steering Committee members were aware that most previous naltrexone studies were 3 months in duration and most acamprosate studies 3 months to 1 year in duration. The main COMBINE Study outcomes would compare
relapse to any drinking and relapse to heavy drinking across treatment groups. Because most relapse is known to occur within 3 months after the initiation of treatment, it was agreed that the study should have a treatment period that was longer than 3 months. Conducting the treatment for 1 year would provide additional safety information on the medication, but would not have added much additional information on relapse. Providing a full year of medication treatment, along with medication management therapy and laboratory monitoring, would have added significantly to the cost of the study, and the available funds did not allow this. Six months of treatment was thought to be an acceptable compromise between 1 year and 3 months. Additional consideration was given as to whether pharmacotherapy should start and/or finish concurrently with psychotherapy. Ultimately, the limited finances available for the study and the 6-year overall time frame for study completion resulted in a further compromise decision: a duration of 4 months for medication treatment, to run concurrently with psychosocial treatment. The latter was conducted conjointly with the pharmacotherapy to help facilitate adherence to the study medications.

Determination of medication dosages

Although naltrexone and acamprosate had each been studied at several dosages in previous clinical trials, there were not much data about the optimal doses for treatment. Consideration was given to conducting a multiple-dose study (i.e., 0, 50 and 100 mg naltrexone and 0, 2,000 and 3,000 mg acamprosate). Although this design would be optimal for determining a dose response of each medication, limitations in the total number of participants would result in cells of a smaller sample size and reduced statistical power, particularly for interaction effects between medications and psychosocial treatments. Because the Steering Committee believed that it was important to determine interaction effects, the study was limited to a single dose of each medication.

Having decided to study just one dose of each medication, the question then became what was the optimal dose of medication to study? Naltrexone had been studied almost exclusively at a dose of 50 mg per day. However, there were suggestions that higher doses of naltrexone might be more efficacious. One study showed that patients with higher (greater than 40 ng/ml) blood levels of beta-naltrexol, a naltrexone metabolite, showed reduced drinking, whereas those with lower naltrexol blood levels did not (McCaul et al., 1997). The Steering Committee was aware that poor medication compliance could affect outcomes; several naltrexone trials showed significant reductions in drinking only when participants who consumed more than 70% of their medication were included (Chick et al., 2000; Monti et al., 2001; Volpicelli et al., 1997). The COMBINE investigators considered that a higher dose of naltrexone (100 mg per day) would be more effective than a lower dose (50 mg per day), because the higher dose would result in higher blood levels of naltrexone and beta-naltrexol; higher blood levels of active medication could result in more opioid receptor blockade and offset the effects of less than perfect compliance.

On the other hand, there were concerns that a higher naltrexone dose might be associated with a greater frequency of side effects, including serious side effects such as liver toxicity. Although very high daily doses (300 mg) of naltrexone were associated with hepatotoxicity, there were little objective data about safety at the 100 mg daily dose. Increased side effects at 100 mg might also lead to decreased compliance, increased medication discontinuation or dropout in the naltrexone groups.

Two studies that utilized 100 mg daily doses of naltrexone supported the higher dose. A safety study that did not assess outcomes used a range of dosages and suggested that 100 mg per day was safe (Croop et al., 1997). Also, the investigators were aware of an ongoing, clinical trial that used 100 mg of naltrexone daily (Monterosso et al., 2001), without increased side effects, hepatotoxicity or dropout at the higher naltrexone dose.

In weighing all of the positive and negative evidence, the COMBINE investigators decided to utilize the 100 mg daily dose of naltrexone. In addition, the investigators believed that conducting a study that utilized a different and a higher naltrexone 100 mg daily dose, as opposed to the generally recognized as effective 50 mg naltrexone dose, would provide important new information about naltrexone dosing and outcomes to alcohol researchers and clinicians.

In the case of acamprosate, there was more evidence for a dose response, with higher doses of acamprosate of 3,000 mg per day showing the treatment efficacy and a good side-effect profile (Mason and Ownby, 2002). Thus, the 3,000 mg dose of acamprosate was chosen for COMBINE.

To test safety of the higher medication doses being considered, two pilot studies were conducted, each at several of the clinical sites. The first pilot was a Phase 2 pharmacokinetic study in which placebo, naltrexone, acamprosate and naltrexone + acamprosate were administered to alcohol-dependent inpatients. Medication doses were titrated up to 100 mg naltrexone and 3,000 mg acamprosate. The results of the first pilot demonstrated that 100 mg doses of naltrexone and 3,000 mg of acamprosate were safe when co-administered together and with alcohol (Johnson et al., 2003). The second pilot study focused on the feasibility of delivering daily naltrexone (100 mg) and acamprosate (3,000 mg) and the two behavioral treatments, individually and in combinations, to 108 alcohol-dependent outpatients, some of whom would also be consuming alcohol (COMBINE Study Research Group, 2003). The results of the second pilot demonstrated that the medications were well tolerated in an
outpatient treatment setting and that the proposed behavioral and pharmacological treatment protocols were compatible.

Dosage titration was another factor considered. Several of the investigators with experience using naltrexone believed that naltrexone should be titrated over 1 week up to the 100 mg dose to minimize side effects associated with beginning naltrexone. Acamprosate does not require titration. A retitration protocol was also developed for persons who stopped their medication for more than 2 weeks and had to restart. A dosage reduction protocol was developed for individuals with significant side effects attributable to medication; receiving reduced medication dosage allowed some individuals to remain on the study, as some medication side effects are dose dependent.

**Determination of dosage form**

The daily doses of medication to be utilized in COMBINE required that eight pills be taken every day: six 500 mg acamprosate tablets or placebo and two 50 mg naltrexone tablets or placebo. This large number of pills potentially imposed a burden of pill taking on the study participants. Moreover, the existence of a titration schedule during Week 1 added further complexity to the dosing, necessitating that initial 25 mg dose of naltrexone be overencapsulated to maintain the blind. Several options were considered for medication dosing methods, including blister packs and electronic monitoring pill bottle caps. The investigators decided to utilize blister packs that contained 1 week’s supply of pills per package. A special pack was utilized for the Week 1 titration. The blister packs were prepared at the Department of Veterans Affairs research pharmacy in Albuquerque, New Mexico, which is experienced in the preparation of medication for clinical trials. The blister-pack layout, which labeled morning, midday and night doses for each day, assisted the participants with compliance and assisted the research staff with counting of pills when the blister packs were returned. Unfortunately, because the blister-pack packaging was novel, the FDA required stability testing, which delayed implementation of the trial by 90 days.

The investigators also developed medication instructions that were distributed to participants. The instructions addressed issues such as what to do for missed doses, potential side effects and other medication use. These and many other compliance and safety issues were discussed in the Medical Management therapy sessions (see Pettinati et al., this supplement).

**Medication availability and regulatory issues**

Because acamprosate was not yet available in the United States and not FDA approved for the treatment of alcohol dependence at the time the COMBINE Study was initiated, it was necessary to apply for an Investigational Drug Exemption from the FDA. This required the support of the manufacturer of acamprosate, Lipha Pharmaceuticals. Lipha agreed to monitor the study for the FDA according to regulatory requirements. In addition, Lipha also agreed to supply the study medications, acamprosate and naltrexone, and matching placebo at no cost for the COMBINE Study.

**Summary**

The process and procedures by which the COMBINE Steering Committee chose the specific pharmacotherapies to be used in the study were lengthy and detailed, but necessary for a study of this magnitude and importance. Many alternatives were considered by the Steering Committee regarding the specific medications to study, the number of doses of each medication, the specific doses utilized, dosage titrations, the duration of medication administration and the methods to monitor safety. A number of compromises were necessary; no single study can answer all questions about pharmacotherapies for alcoholism. The results of the decision making with respect to medications and safety monitoring resulted in a well-planned and well-executed study that minimized risks to the participants.

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**Disclosure**

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