

Brief Report



The COMBINE Study—

An Overview of the Largest Pharmacotherapy Study to Date for Treating Alcohol Dependence

by Helen M. Pettinati, PhD; Raymond F. Anton, MD;
and Mark L. Willenbring, MD

Treatment for alcohol dependence in the 21st century has the option of adding pharmacotherapy to traditional treatment approaches, which have primarily included drug and alcohol counseling, newer specialized behavioral therapies, and support groups. While alcohol treatment outcomes

with counseling or behavioral treatments are better than what most people think,¹ relapse rates remain unacceptably high given the devastation caused by the illness. The growing knowledge of alcohol's neurobiological effects on the brain has led to both the development of promising pharmacotherapies that can be

added to counseling in treating alcohol disorders and a series of controlled trials to evaluate the impact of combining medications with counseling or behavioral treatments.

Currently, there are four medications that have been approved by the Food and Drug Administration (FDA) for use in treating alcohol dependence: Disulfiram (Antabuse®), oral naltrexone (Revia®), acamprosate (Campral®), and an intramuscular (IM) once-a-month naltrexone injection (Vivitrol®). [For a summary of these medications, see the brief report in the May issue of *Psychiatry 2006*.²]

In the May 3, 2006, issue of the *Journal of the American Medical Association*, Anton and colleagues³ reported results from the largest known controlled pharmacotherapy clinical trial for treating alcohol dependence, i.e., the COMBINE study, which was supported by the National Institute on Alcohol Abuse and Alcoholism. This study evaluated the efficacy of specific pharmacotherapies, behavioral or psychosocial interventions, and their combinations for the treatment of alcohol dependence. The COMBINE study evaluated treatment response to novel medication and psychosocial treatment combinations for 1,383 alcohol-dependent, treatment-seeking patients from 11 US sites. What follows is a brief summary of the design and results of the COMBINE study. Detailed information on the study's conceptual, methodological, and practical issues are available in a supplement to the *Journal of Studies on Alcohol*.⁴

In the COMBINE study, alcohol-dependent patients were randomly assigned for four months to

[b r i e f r e p o r t]

placebo pills and/or one or two medications given in combination as 3g/day of acamprosate and/or 100mg/day of naltrexone, both of which are currently approved by the FDA for treating alcohol dependence. The FDA approval specifies slightly lower doses of these drugs: 2g/day of acamprosate and 50mg/day of naltrexone. Acamprosate is thought to be a brain glutamate receptor stabilizer that promotes abstinence by alleviating the physical and psychological discomfort (sweating, anxiety, and sleep disturbances) experienced by many alcohol-dependent individuals once they stop drinking. Naltrexone is an opioid receptor antagonist that is thought to reduce the reward or excitement associated with drinking alcohol and/or coming in contact with alcohol-related cues in the environment (anticipatory excitement). Thus, given their different purported mechanisms of action on drinking, there was a plausible rationale for investigating potential synergistic “outcome-enhancing” effects of these medications in combination.⁵ Slightly higher doses of these medications were prescribed in the COMBINE study because prior data suggested that higher daily dosages might provide better efficacy.⁶ However, there was flexibility in this study for clinicians to lower daily doses for any patients who could not tolerate the maximum target daily dose. In fact, the average daily dose of active medications in this study was 88mg of naltrexone and 2,537mg of acamprosate.

In the COMBINE study, all medication or placebo pills prescribed were given in the context of a maximum of nine manual-guided counseling visits

across four months, delivered by medical practitioners, i.e., medical management (MM).⁷ Other than the first MM visit, which was approximately 45 minutes in length, the eight follow-up MM visits were approximately 20 minutes each. The medical clinicians who delivered MM used an easy-to-follow manual⁸ to provide their patients with education about their disease and potential treatments, to give patients advice for reducing drinking, to inquire about any medication side-effects, and to emphasize the importance of routinely taking medications as prescribed. Following this systematic approach reflected in the MM manual, clinicians would spend part of the time with the patient at each visit reviewing pill-taking practices, and, when indicated, the clinician would discuss with the patient ways to improve pill adherence.

In addition, one-half of the patients taking medication also received manual-guided, specialty alcohol therapy, i.e., combined behavioral intervention (CBI),^{9,10} for up to approximately twenty 50-minute sessions (the median number of CBI sessions actually attended by patients in the 4-month trial was 10). CBI was specially developed by a subgroup of COMBINE investigators to include a strategic “meld” of prior proven behavioral treatments, e.g., motivational enhancement

therapy¹¹ and cognitive behavioral therapy.¹² By providing specialty therapy to only half of the patients taking medications, this study was designed to assess the advantages of combining specialty treatment with pharmacotherapy. In the COMBINE study, all counseling visits (MM or CBI) were audiotaped, with a proportion rated by independent listeners to ensure clinician adherence to the expected treatment content.¹³ Finally, to evaluate the impact of taking pills (in this case, placebo pills) on the effectiveness of specialty treatment, one group of patients received the specialty treatment (CBI) without being asked to take any pills.¹⁴

Thus, any given patient could be assigned to one of nine different treatments. The nine treatments were naltrexone in combination with acamprosate, with or without CBI (2 treatment conditions); naltrexone in combination with placebo pills, with or without CBI (2 treatment conditions); acamprosate in combination with placebo pills, with or without CBI (2 treatment conditions); placebo pills only, with or without CBI (2 treatment conditions); and CBI with no pills (1 treatment condition).

The results of the COMBINE study are as follows: First, many of the patients benefited by participating in the study because all nine groups had a substantial reduction in days of drinking, i.e.,

...given their different purported mechanisms of action on drinking, there was a plausible rationale for investigating potential synergistic “outcome-enhancing” effects of [acamprosate and naltrexone] in combination.

"...the results of the COMBINE study demonstrated that...naltrexone, when given with medical counseling that emphasizes taking medications as prescribed, can yield clinically significant outcomes...that are either as compelling, and under some conditions, more compelling than those observed with specialty behavioral therapy."

more abstinent days over the four months of treatment, compared to pretreatment drinking levels. However, not all patient groups reported similar outcome rates. That is, the patient groups who demonstrated the best (statistical) drinking outcomes after 16 weeks of outpatient treatment had received naltrexone with MM counseling alone (no specialty CBI) or had received specialty therapy, CBI, with just the placebo pills and MM counseling. There was no advantage found in the COMBINE study for adding acamprosate either to MM or to specialty alcohol treatment (CBI). This acamprosate result is puzzling, given the many European studies that have reported an acamprosate effect (over placebo) for maintaining abstinence from alcohol.¹⁵ Also, the group that received specialty treatment (CBI) without pills, i.e., no placebo pills or active medication, demonstrated the poorest outcomes—a reminder of the powerful "placebo" effects that are anticipated in controlled clinical trials and why double-blinded, placebo-controlled designs are important in evaluating true medication effects.

Thus, the results of the COMBINE study demonstrated

that a pharmacotherapy, like naltrexone, when given with medical counseling that emphasizes taking medications as prescribed, can yield clinically significant outcomes (reduced drinking/increased abstinence) that are either as compelling, and under some conditions, more compelling than those observed with specialty behavioral therapy. One important implication of the COMBINE results is that naltrexone with MM can be delivered in healthcare settings where traditional specialty treatment is unavailable. Receiving treatment directly from their primary healthcare provider could greatly expand treatment options for persons with an alcohol disorder.

About eight million people in the US are alcohol dependent, with more than that figure meeting diagnostic criteria for alcohol abuse.¹⁶ However, most of these people are not receiving appropriate treatment.¹⁷ Alcohol dependence is the third leading preventable cause of morbidity and mortality and a major contributor to healthcare costs in this country.¹⁸ The results of the COMBINE study provide important information to the professional community that will undoubtedly

change the way we think about and treat alcohol disorders as we make our way through the 21st century.

REFERENCES

1. Miller WR, Wilbourne PL, Mesa Grande: A methodological analysis of clinical trials of treatments for alcohol use disorders. *Addiction* 2002;97(3):265-77.
2. Pettinati HM, Rabinowitz AR. New pharmacotherapies for treating the neurobiology of alcohol and drug addiction. *Psychiatry* 2006;3(5):14-16.
3. Anton RF, O'Malley SS, Ciraulo DA, et al. Combined pharmacotherapies and behavioral interventions for alcohol dependence: The combine study: A randomized controlled trial. *JAMA* 2006;295(17):2003-17.
4. Pettinati HM, Zweben A, Mattson ME (eds). The COMBINE study: Conceptual, methodological, and practical issues in a clinical trial that combined medications and behavioral treatments. *J Stud Alcohol Suppl* 2005;(15)
5. Mason BJ. Rationale for combining acamprosate and naltrexone for treating alcohol dependence. *J Stud Alcohol Suppl* 2005;(15):148-56; discussion 140.
6. Swift R, Pettinati HM. Choosing pharmacotherapies for the COMBINE study-- process and procedures: An investigational approach to combination pharmacotherapy for the treatment of alcohol dependence. *J Stud Alcohol Suppl* 2005;15:141-7.
7. Pettinati HM, Weiss RD, Dundon W, et al. A structured approach to medical management: A psychosocial intervention to support pharmacotherapy in the treatment of alcohol dependence. *J Stud Alcohol Suppl* 2005;15:170-8.
8. Pettinati HM, Weiss RD, Miller WR, et al. COMBINE Monograph Series, Volume 2. *Medical Management Treatment Manual: A Clinical Research Guide for Medically Trained Clinicians Providing Pharmacotherapy as Part of the Treatment for Alcohol Dependence*. DHHS Publication No (NIH) 04-5289. Bethesda, MD: NIAAA, 2004.
9. Longabaugh R, LoCastro J, Miller WR, Zweben A. Origins, issues and options in the development of the Combined Behavioral Intervention. *J Stud Alcohol Suppl* 2005;15:179-87.

[b r i e f r e p o r t]

10. Miller WR (ed). COMBINE Monograph Series, Volume 1. *Combined Behavioral Intervention Manual: A Clinical Research Guide for Therapists Treating People with Alcohol Abuse and Dependence*. DHHS Publication No. (NIH) 04-5288. Bethesda, MD: NIAAA, 2004.
11. Miller WR, Zweben A, DiClemente CC, Rychtarik RG. Project MATCH Monograph Series, Volume 2. *Motivational Enhancement Therapy Manual: A Clinical Research Guide for Therapists Treating Individuals with Alcohol Abuse and Dependence*. DHHS Publication No. 92-1894. Rockville MD: NIAAA, 1992.
12. Kadden R, Carroll KM, Donovan D, et al. Project MATCH Monograph Series, Volume 3. *Cognitive-behavioral Coping Skills Therapy Manual: A Clinical Research Guide for Therapists Treating Individuals with Alcohol Abuse and Dependence*. DHHS Publication No. 92-1895. Rockville, MD: NIAAA, 1992.
13. Miller WR, Moyers TB, Arciniega L, et al. Training, supervision and quality monitoring of the COMBINE study behavioral interventions. *J Stud Alcohol Suppl* 2005;15:188-95.
14. Weiss RD, LoCastro JS, Swift R, et al. The use of a "psychotherapy with no pills" treatment condition as part of a combined pharmacotherapy-psychotherapy research study of alcohol dependence. *J Stud Alcohol Suppl* 2005;15:43-9.
15. Mann K, Leher P, Morgan MY. The efficacy of acamprosate in the maintenance of abstinence in alcohol-dependent individuals: results of a meta-analysis. *Alcohol Clin Exp Res* 2004;28(1):51-63.
16. Grant BF, Dawson A, Stinson FS. The 12-month prevalence and trends in DSM-IV alcohol abuse and dependence: United States, 1991-1992 and 2001-2002. *Drug Alcohol Depend* 2004;74:223-34.
17. McGlynn EA, Asch SM, Adams J, et al. The quality of health care delivered to adults in the United States. *NEJM* 2003;348(26):2635-45.
18. Mokdad AH, Marks JA, Stroup DF et al. Actual causes of death in the United States, 2000. *J Am Med Assoc* 2004;291:1238-45. ●

Dr. Pettinati is Professor, Department of Psychiatry, University of Pennsylvania School of Medicine, Philadelphia; Dr. Anton is Distinguished University Professor and Professor of Psychiatry, Medical University of South Carolina, Charleston; and Dr. Willenbring is Director of Treatment and Recovery Research, National Institute on Alcohol Abuse and Alcoholism/National Institutes of Health, Bethesda, Maryland.

Address correspondence to: Helen M. Pettinati, PhD, University of Pennsylvania Treatment Research Center, 3900 Chestnut Street, Philadelphia, PA 19104; Phone (215) 222-3200; Fax: (215) 386-5106; E-mail: Pettinati_H@mail.trc.upenn.edu

FINANCIAL DISCLOSURES: Dr. Pettinati has received grant/research support from Alkermes, AstraZeneca, Bristol-Myers Squibb, Cephalon, Forest Laboratories, and Ortho McNeil, and is a consultant or on the advisory board/speakers bureaus for Alkermes, AstraZeneca, Cephalon, and Forest Laboratories. Dr. Anton has received grant/research support from Bristol-Myers Squibb, Contra Pharma/Biotie Pharmaceuticals, Hythiam, Johnson & Johnson, Ortho McNeil, and Pfizer, and is a consultant or on the advisory board/speakers bureaus for Alkermes, AstraZeneca, Axis-Shield, Bristol-Myers Squibb, Cephalon, Contra Pharma/Biotie Pharmaceuticals, Drug Abuse Sciences, Forest Laboratories, Hythiam, Pfizer, and Sanofie-Aventis. Dr. Willenbring has no relevant industry relationships to disclose.



You've read the research...now read *Psychiatry 2006* to learn how to apply that research so you can better treat your patients.

Psychiatry 2006 is a peer-reviewed journal that provides evidence-based information to practicing clinicians—information clinicians can apply to their daily practices. So, read the research journals...and read *Psychiatry 2006* to learn how to use the research to better treat your patients.

Psychiatry²⁰⁰⁶
read. learn. apply.

www.psychiatry2006.com

To submit an article for peer review, contact:

Elizabeth A. Klumpp
Executive Editor
Phone 610.325.9905
Fax 610.325.9906
eklumpp@matrixmedcom.com



MATRIX MEDICAL COMMUNICATIONS
PO BOX 445 • EDMONT, PA 19028-
0445 866.325.9907