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...
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 [acamprosate and naltrexone] in combination.

Slightly higher doses of these medications were prescribed in the COMBINE study because prior data suggested that higher daily dosages might provide better efficacy. 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). 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 manual 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), 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 therapy and cognitive behavioral therapy. 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. 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. 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.,...
“...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 abstinence 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


