The Challenge to Find Effective Therapies for Patients with Alcohol Dependence

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;295:2003–17.

Study Overview

Objective. To evaluate the efficacy of medications and behavioral therapy individually or in combination to treat alcohol dependence and to evaluate the placebo effect on overall outcome.

Design. Randomized controlled trial.

Setting and participants. 1383 recently alcohol-abstinent volunteers (428 women and 955 men; median age, 44 years) from 11 U.S. academic sites with a DSM-IV diagnosis of primary alcohol dependence were enrolled from January 2001 through January 2004.

Intervention. Patients were assigned to medical management (MM) and 16 weeks of either (1) naltrexone (100 mg/day), (2) acamprosate (3 g/day), (3) both, or (4) placebo, with or without a combined behavioral intervention (CBI), resulting in 8 groups. A ninth group received CBI alone (no pills or MM). Patients were also encouraged to attend community Alcoholics Anonymous (AA) meetings and were followed for up to 1 year after treatment.

Main outcome measures. Percent days abstinent from alcohol and time to first heavy drinking day.

Main results. 71% of patients had at least 12 years of education, and 23% were minorities. Follow-up rates ranged from 80% to 87% without significant differences across groups (mean medication adherence rate, 86%). Attendance at therapy sessions averaged 50%, while AA attendance rates ranged from 17% to 35%. Patients who received naltrexone (n = 302), naltrexone and CBI (n = 309), or placebo and CBI (n = 305) had higher percent days abstinent (80.6, 77.1, and 79.2, respectively) than those receiving placebo and no CBI (n = 305; percent days abstinent, 75.1). In addition, naltrexone reduced risk of return to heavy drinking (hazard ratio, 0.72 [97.5% confidence interval, 0.53–0.98]; P = 0.02) over time. Acamprosate alone or in any combination with naltrexone and CBI showed no significant effect on drinking versus placebo. Those receiving CBI without pills or MM (n = 157) had lower percent days abstinent (66.6) than those receiving placebo plus MM (n = 153; 73.8 percent days abstinent) or placebo plus MM and CBI (n = 156; 79.8 percent days abstinent) (P < 0.001). After 1-year follow-up, results were not significant but showed similar trends.

Conclusion. Patients receiving MM combined with naltrexone, CBI, or both had more days of alcohol abstinence. Acamprosate, with or without CBI, was not effective. Placebo with CBI is more effective than CBI alone, suggesting a significant placebo effect.

Commentary

An estimated 8 million adults in the United States [1] meet the DSM-IV criteria for diagnosis of alcohol dependence, but

only a small number of these individuals seek treatment. Of those who do, most are referred to community groups such as AA, and few receive medication specifically shown to treat alcohol dependence. Until recently, disulfiram was the only available medication approved for alcohol dependence, and its side effects made it very unpopular in the primary care setting. In 1994, the U.S. Food and Drug Administration approved naltrexone for the treatment of alcohol dependence. This was followed in 2004 by the approval of acamprosate, a drug that has been used in Europe for treatment of alcohol dependence for a decade. Meta-analyses of European studies that evaluated acamprosate indicated that the drug helped alcohol-dependent individuals maintain abstinence once they had stopped drinking [2,3].

At the time Anton and colleagues started the COMBINE study, acamprosate was investigational in the United States; hence, this trial in part sought to determine the efficacy of acamprosate in the treatment of alcohol dependence, specifically to maintain abstinence. This study is a complex, randomized, placebo-controlled trial of naltrexone, acamprosate, naltrexone/acamprosate combined, and double placebo groups with and without a combined high-intensity psychosocial behavioral therapy intervention for the treatment of alcohol dependence. One of 9 groups received only CBI, which mimics prevalent practice and served to evaluate for placebo effect. In addition, the 8 groups that took pills had a low-intensity medical management follow-up similar to routine primary care in the community.

Interestingly, while naltrexone alone and placebo plus CBI both significantly increased the percent of abstinent days, combining naltrexone with CBI did not show an additive effect. Also surprising was the significant effect of placebo plus CBI when compared with CBI alone, indicating a substantial placebo effect. In addition, acamprosate either alone or in combination with naltrexone did not show any advantages over placebo. Lastly, treatment effects were diminished and differences among groups were no longer statistically significant at 1-year follow-up, although the findings showed similar trends. This suggests that research into longer duration therapies is warranted to further improve treatment of alcohol dependence.

Applications for Clinical Practice

Primary care physicians who have patients with alcohol dependence may consider naltrexone in the context of routine medical management to help patients maintain sobriety.

—Review by Mark S. Horng, MD

References

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