Treatments for Alcohol Dependence: Rethinking the Role of Comorbidity and Clinical Subtypes

This issue of the *Journal* includes two articles that address treatment of alcohol dependence. Pettinati et al. (1) report a 14-week, randomized controlled trial comparing naltrexone alone, sertraline alone, combination of naltrexone and sertraline, and placebo as adjunct to weekly cognitive-behavioral therapy (CBT) for depressed alcohol-dependent patients. Johnson (2) presents a look to the future on medication-assisted treatment strategies for three different clinical phenotypes of alcohol-dependent patients. This excellent review reminds us that alcoholism is a complex heterogeneous disorder with identified genetic and environmental risk factors. Alcohol-related disorders affect male and female patients alike, both young and old. Family history, early exposure to alcohol, and comorbidity are important contributors to the future risk of developing alcoholism, severity of the disorder, and response to treatment.

The comorbidity of alcohol use disorders and independent major depressive disorder has long been acknowledged, but treatment guidelines, in particular pharmacotherapeutic approaches for patients with both conditions, have remained unclear. Clinicians treating a depressed alcoholic patient have not had empirical data on whether antidepressant and antialcohol medications, singly or in combination, reduce the symptoms of either or both disorders.

"Comorbidity of alcohol use disorders and independent major depressive disorder has long been acknowledged, but treatment guidelines…have remained unclear."

The study by Pettinati et al. provides some answers. This is an excellent study with a real-world outpatient sample, 87% medication adherence rate, and higher target doses to minimize suboptimal dosing. The naltrexone plus sertraline group performed much better on both alcohol-related primary outcome measures compared with the naltrexone alone, sertraline alone, and placebo groups combined. Overall, the percentage of patients who achieved abstinence in the combination group was twice that of the other groups. The median time to return to heavy drinking was three and one-half times longer with combination treatment than with other treatment conditions. Notably, secondary analyses showed a positive effect of the combination regimen on heavy drinking. Perhaps not unexpectedly, considering the severity of depression and short duration of treatment, the results were less impressive for depression-related outcomes. The naltrexone plus sertraline group did not show superiority over other groups in either the overall change in Hamilton Depression Rating Scale (HAM–D) scores or end-of-treatment HAM–D scores, although there was a nearly significant difference toward a higher remission rate in the last 3 weeks of the trial in the combination group.

These findings should be interpreted in the context of several limitations. This was a single-site trial with a highly experienced clinical research team. Also, over 50% of screened subjects were excluded, in particular subjects receiving existing antidepressants or other psychotropic drugs. It is important to note that the medications were adjunctive to weekly CBT sessions, the doses of naltrexone and sertraline were higher than the Food and Drug Administration (FDA)-recommended doses for initial treatment, and a minimum of 3 days of abstinence from alcohol was required prior to initiating the medications. It would have been interesting to know whether there were beneficial

effects of the combination treatment on elevated gamma-glutamyl transpeptidase and whether there was a reduction in the number of heavy drinking days during the trial.

While the findings of Pettinati et al. need to be replicated in a larger multisite trial, there are clinical lessons to be learned. It appears reasonable to combine naltrexone with a selective serotonin reuptake inhibitor (SSRI) such as sertraline for treatment-ready patients with alcohol dependence and comorbid major depression. In such patients, medications should be combined with behavioral interventions such as CBT, as was the case in this study. For appropriate patients, it may not be necessary to wait for prolonged abstinence before instituting pharmacotherapy. For patients without tolerability issues, it may be worth titrating the naltrexone to a dose of 100 mg/day and the SSRI to the maximum therapeutic dose and then treating for at least 12 weeks to evaluate adequate response. Based on this study, it is difficult to justify use of an SSRI alone in the absence of concurrent behavioral interventions and pharmacotherapy for the alcoholic patient with major depression.

The article by Johnson offers treatment recommendations for three clinical subtypes of alcohol dependence and reviews the evidence in support of the recommendations. The article rightly points out the importance of early identification of at-risk drinkers through standardized screening tools such as the Alcohol Use Disorders Identification Test (AUDIT) recommended by the National Institute on Alcohol Abuse and Alcoholism Clinicians Guide (3). For those who are identified as at-risk drinkers, a more detailed history about the pattern of drinking, associated medical and psychiatric comorbidities, family history, and sufficient clinical information to make a DSM–IV diagnosis should be obtained. In the case of the middle-aged man who has severe chronic alcohol dependence with regular and frequent heavy drinking and medical complications, a trial with topiramate (25–300 mg/day with a target dose of ≥100 mg/day) is recommended. For the young adult man with early-onset drinking, antisocial behavior, binge drinking, and emerging alcohol dependence, low-dose ondansetron (4 μg/kg) or oral naltrexone, up to 100 mg/day, along with brief intervention is considered appropriate. Finally, for an elderly, recently retired woman who feels gloomy and is drinking to alleviate her low mood, long-acting injectable naltrexone, 380 mg once a month for 4 months, is recommended along with brief intervention.

The article has much practical advice for clinicians who may not be specialized in treating alcoholism. First, always take a drinking history and negotiate a drinking goal. While the most favorable outcome is total abstinence or delay of relapse to heavy drinking, many patients need to be helped toward this goal by setting lower levels of drinking. Second, the mainstay of treatment is some form of psychosocial or brief intervention. Clinical monitoring can be successfully managed by nonspecialist practitioners in office-based settings. Third, pairing appropriate pharmacotherapy based on its mechanism of action in blocking positive and/or negative reinforcement pathways of ethanol self-administration behavior can effectively improve treatment outcome.

Currently, four FDA-approved medications are available to treat alcohol dependence: disulfiram, oral naltrexone, injectable naltrexone, and acamprosate. Topiramate and ondansetron are not yet FDA approved, and therefore their use should be considered off-label. As Johnson illustrates, both the oral and injectable naltrexone preparations may be preferred for different clinical subphenotypes. Data from the Combined Pharmacotherapies and Behavioral Interventions for Alcohol Dependence (COMBINE) trial provide some support for the differential efficacy of naltrexone for clinical subphenotypes (4, 5). Acamprosate has an excellent tolerability profile, and may have a therapeutic role in certain situations, in particular during the postdetoxification phase (6). Problems with compliance and patient acceptance have limited the clinical effectiveness of disulfiram. However, it may be beneficial in a selected group of patients where medication compliance can be supervised.

Choosing the right medication for alcohol dependence should be guided by risk-benefit profile, patient preference, cost-effectiveness, and physician familiarity with the

drug. Tailoring medications to fit clinical domains in alcohol dependence is an attractive concept, but scientific data for its support are still in infancy. Future studies such as the PREDICT trial (7) that investigate the relationship between clinically relevant phenotypes and biological markers with treatment response in alcohol dependence could help to individualize treatment for alcohol dependence. The diagnostic criteria and terminologies for alcohol dependence in the upcoming DSM–5 may change. The "Substance-Related Disorders" category has been proposed to be tentatively retitled "Addiction and Related Disorders" (8).

References

1. Pettinati HM, Oslin DW, Kampman KM, Dundon WD, Xie H, Gallis TL, Dackis CA, O'Brien CP: A double-blind, placebo-controlled trial combining sertraline and naltrexone for treating co-occurring depression and alcohol dependence. Am J Psychiatry 2010; 167:668–675
2. Johnson BA: Medication treatment of different types of alcoholism. Am J Psychiatry 2010; 167:630–639
3. National Institute on Alcohol Abuse and Alcoholism: Helping Patients Who Drink Too Much: A Clinician's Guide. Bethesda, Md, National Institute of Health, National Institute on Alcohol Abuse and Alcoholism, 2005
4. Anton RF, O'Malley SS, Ciraulo DA, Cisler RA, Couper D, Donovan DM, Gastfriend DR, Hosking JD, Johnson BA, LoCastro JS, Longabaugh R, Mason BJ, Mattson ME, Miller WR, Pettinati HM, Randall CL, Swift RM, Weiss RD, Williams LD, Zweben A; COMBINE Study Research Group: Combined pharmacotherapies and behavioral interventions for alcohol dependence: the COMBINE study: a randomized controlled trial. JAMA 2006; 295:2003–2017
5. Bogenschutz MP, Scott Tonigan J, Pettinati HM: Effects of alcoholism typology on response to naltrexone in the COMBINE study. Alcohol Clin Exp Res 2009; 33:10–18
6. Kampman KM, Pettinati HM, Lynch KG, Xie H, Dackis C, Oslin DW, Sparkman T, Sharkoski T, O'Brien CP: Initiating acamprosate within-detoxification versus post-detoxification in the treatment of alcohol dependence. Addict Behav 2009; 34:581–586
7. Mann K, Kiefer F, Smolka M, Gann H, Wellek S, Heinz A; PREDICT Study Research Team: Searching for responders to acamprosate and naltrexone in alcoholism treatment: rationale and design of the PREDICT study. Alcohol Clin Exp Res 2009; 33:674–683
8. American Psychiatric Association: Proposed Draft Revisions to DSM Disorders and Criteria. Arlington, Va, American Psychiatric Association, 2010. http://www.dsm5.org/Pages/Default.aspx

ASHWIN A. PATKAR, M.D.
TING-KAI LI, M.D.

Address correspondence and reprint requests to Dr. Patkar, Duke University Medical Center, Box 3063, Durham, NC 27710; ashwin.patkar@duke.edu (e-mail). *Editorial accepted for publication March 2010 (doi: 10.1176/appi.ajp.2010.10030309).*

Dr. Patkar has received research/grant support from Abbott; Forest Pharmaceuticals, which markets acamprosate; Lundbeck; Merck; Ortho-McNeil Pharmaceuticals, manufacturer of topiramate; Pfizer, manufacturer of sertraline; Titan Pharmaceuticals; and Shire. Dr. Patkar also has received consultant honoraria from Bristol-Myers Squibb and Reckitt Benckiser; serves on the speaker's bureaus for Alkermes, which manufactures injectable naltrexone, and Pfizer; and has received advisory board fees or CME honoraria from Bristol-Myers Squibb, Merck, and Reckitt Benckiser. Dr Li reports no financial relationships with commercial interests. Dr. Freedman has reviewed this editorial and found no evidence of influence from these relationships.