PRACTICAL PSYCHOPHARMACOLOGY

Drug Therapy for Alcohol Dependence

Alcohol dependence is among the most common psychiatric disorders: A recent National Epidemiologic Survey on Alcohol and Related Conditions found a 12-month prevalence of 3.8% (Arch. Gen. Psychiatry 2007;64:830-42). In individuals with comorbid psychiatric diagnoses, the rate is higher.

There is growing evidence of efficacy for office-based pharmacotherapy—an approach endorsed by the National Institute on Alcohol Abuse and Alcoholism.

Four medications have thus far been approved by the Food and Drug Administration for alcohol dependence, and the Combined Pharmacotherapies and Behavioral Interventions (COMBINE) study, a government-supported multicenter trial, found that one of them (naltrexone), when given with a modest program of medical management, was as effective as specialized behavioral treatment in preventing relapse (JAMA 2006;295:2003-17).

"Medication should be offered to all alcohol-dependent patients who see a psychiatrist," said Dr. Robert Swift, professor of psychiatry and human behavior at Brown University, Providence, R.I., and associate chief of staff for research at the Providence Veterans Affairs Medical Center.

The more severe the disorder, the stronger the argument for pharmacotherapy, said Dr. Henry Kranzler, professor of psychiatry at the University of Connecticut, Farmington. "It is certainly indicated for anyone who has failed at any psychosocial treatment."

The FDA-approved drugs—disulfiram (Antabuse), two forms of naltrexone (tablet and extended release injectable suspension), and acamprosate (Campral)—have different mechanisms and are presumably best suited to different groups of patients. "One problem is that evidence-based data on patient-treatment matching are scant, compared to the data for antidepressants and antipsychotics in affective and psychotic disorders," Dr. Swift said, "although some can be gleaned from pharmacotherapy studies."

None of these drugs appears to interact with agents commonly used for other disorders and may be prescribed concurrently, he said.

Disulfiram, the oldest of the four, causes accumulation of acetaldehyde, a toxic metabolite of alcohol, which produces a constellation of unpleasant symptoms. It is not a psychotropic but "a psychological deterrent," said Dr. Kyle Kampman, medical director of the Charles O'Brien Center for Addiction Treatment at the University of Pennsylvania, Philadelphia.

Adherence to disulfiram treatment is notoriously poor—around 20%, according to Dr. Kampman. The drug has the best chance of success in individuals who are highly motivated to avoid alcohol, particularly when medication use can be supervised.

Naltrexone apparently blocks the euphoric effect of endogenous opioids released by alcohol. It seems most effective for individuals with high levels of craving and a family history of alcohol dependence. Better social adjustment and later onset also were associated with response in some trials, and genetic studies have linked a particular variant of an opioid receptor gene with successful naltrexone treatment, Dr. Swift noted.

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"Naltrexone certainly helps to sustain abstinence, but it probably works better in reducing heavy drinking," said Dr. Kranzler. "It is a good choice for a patient who wants to cut back but isn't willing to make a commitment to abstinence."

The drug carries a black box warning about liver damage: It should not be given to patients with severe liver disease, and its use requires periodic monitoring of liver enzymes.

Acamprosate appears to normalize glutamate receptors that had been upregulated by chronic alcohol use. Glutamate dysregulation ostensibly plays a role in withdrawal, and the drug has been found most effective for those who experience severe and protracted withdrawal symptoms.

Approval of acamprosate was based on European studies, but the drug has been disappointing in American trials. The differences between European and American samples suggest that acamprosate might work better with heavier drinkers and after more prolonged abstinence.

The different mechanisms of naltrexone and acamprosate might, in theory, complement each other, but data on combining medications are sparse. Dr. Kampman said he sometimes adds the second drug if response to the first is inadequate. In particularly severe cases, he might initiate both simultaneously.

Adherence to medication deserves particular attention. "There's a great sense of denial with chronic disease generally, and alcoholism in particular," said Helen Pettinati, Ph.D., professor of psychiatry at the University of Pennsylvania, Philadelphia.

Dr. Pettinati advises a proactive approach that anticipates adherence difficulties, explores misguided medication attitudes, and promotes optimism for recovery. "Get the patient to talk about problems that arise with pill taking and treatment attendance, as if these are as important as not drinking," she said. "There's often a dialogue in patients' heads about how they're 'better now' and don't need the medication. If they still have some cravings, they tell themselves the medication is not working. Let them know that you understand that dialogue, and get them to talk about it."

Vivitrol, the injectable long-acting formulation of naltrexone, can largely circumvent adherence difficulties. "Patients are very gung ho when they first come in for treatment but often drop out a week or two later," she said. "With Vivitrol, they will have 30 days to experience what the drug can do." In a large clinical trial, the great majority came back for a second injection.

Dr. Pettinati would offer the long-acting formulation with counseling at the outset of treatment to any patient with alcohol dependence. "I don't want to give any patient a failure, and a 30-day injection of naltrexone coupled with counseling gives every person a fighting chance of success," she said.

Nausea can occur with naltrexone, including the injectable form. "It goes away pretty quickly, and it's usually much worse with the first than subsequent shots," so patients should be reassured accordingly, Dr. Kampman said.

The proper duration of treatment is uncertain, but it should be long enough for the patient to achieve lifestyle changes that will support sobriety—perhaps several years of abstinence, Dr. Kampman suggested.

"Physicians make two mistakes in alcohol pharmacotherapy," Dr. Kranzler said. "They don't offer it to patients often enough. Even if benefits are modest, adverse effects are minimal, so patients should not be deprived of a potential advantage. And they don't give the patient an adequate trial on the medication. I'd use at least 2 g and as much as 3 g daily of acamprosate or 100-150 mg of oral naltrexone for 6 weeks, and two injections of long-acting naltrexone, before concluding that medication is exerting no beneficial effect."

It is generally agreed that psychosocial treatment or support should accompany pharmacotherapy. The manual for medication management used in the COMBINE trial is available at http://pubs.niaaa.nih.gov/publications/combine/index.htm.

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Dr. Kranzler has received honoraria for consulting from Elbion GmbH, Sanofi-Aventis, Solvay Pharmaceuticals Inc., H. Lundbeck A/S, and Alkermes, and research support from Bristol-Myers Squibb.

Dr. Kampman is on speakers bureaus for Forest Laboratories, Reckitt Benckiser Group PLC, and Cephalon, and has received grant support from Alkermes.

Dr. Pettinati has received honoraria from Alkermes, AstraZeneca, and Cephalon for consultation on research protocols and analyses of study results, and grant/research support from Alkermes, AstraZeneca, Bristol-Myers Squibb, Cephalon, Forest Laboratories, Eli Lilly & Co., Ortho-McNeil, and Titan Pharmaceuticals Inc. ■

By Carl Sherman, contributing writer

Smoking Associated With Cognitive Decline in Middle Age

BY MARY ANN MOON
Contributing Writer

Smoking is associated with a decline in reasoning ability and with memory deficit as early as in middle age, according to a study of more than 5,000 people.

People who quit smoking before they reach middle age, however, show little of this adverse effect on cognition, according to Severine Sabia of the National Institute for Health and Medical Research at Paul Brousse Hospital in Villejuif, France, and her associates.

Previous studies concluded that smoking is a risk factor for dementia in older adults; it is thought to act primarily through its adverse effect on the vasculature. In this study, the investigators used data from the Whitehall II study to examine the relation of smoking to earlier cognitive impairment, before the onset of dementia.

"Cognition in midlife is clinically relevant because research suggests that individuals with mild cognitive impairment progress to clinically diagnosed dementia at an accelerated rate," Ms. Sabia and her associates noted (Arch. Intern. Med. 2008;168:1165-73).

The Whitehall II study was a longitudinal assessment of socioeconomic factors and health among more than 10,000 British civil servants aged 35-55 years at baseline in 1985-1988.

The subjects were followed at intervals through 2002-2004.

For this study, data were analyzed for a subset of 5,388 participants who underwent evaluation of cognitive function and who furnished a complete smoking history. Short-term verbal memory, inductive reasoning, vocabulary, and verbal fluency were assessed using a battery of standardized tests.

The study participants were categorized as never smokers (2,543 subjects), current smokers (815 subjects), long-term exsmokers (1,519 subjects who had quit before 1985), and recent exsmokers (511 subjects who quit smoking after the study began).

Current smokers were more likely to show deficits, as well as a decline over time in the performance of memory, reasoning, and verbal fluency tasks, than were never smokers.

However, the investigators found no dose-response relationship between the number of pack-years of smoking and cognitive decline. ■