LESSONS LEARNED AT THE INTERFACE OF MEDICINE AND PSYCHIATRY

The Psychiatric Consultation Service at Massachusetts General Hospital (MGH) sees medical and surgical inpatients with comorbid psychiatric symptoms and conditions. Such consultations require the integration of medical and psychiatric knowledge. During their thrice-weekly rounds, Dr. Huffman and Dr. Stern discuss the diagnosis and management of conditions confronted. These discussions have given rise to rounds reports that will prove useful for clinicians practicing at the interface of medicine and psychiatry.

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Disulfiram Use in an Elderly Man With Alcoholism and Heart Disease: A Discussion

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Have you ever wondered how and when to use disulfiram to prevent alcohol relapse? Have you ever considered how disulfiram therapy fits into the overall care of an individual afflicted with alcoholism? What follows is a brief case history, accompanied by a discussion of the safe and efficacious use of disulfiram. An annotated bibliography is appended for those who desire additional information on the topic.

Case Presentation

Mr. A, a 72-year-old former insurance salesman with a history of alcohol dependence and depression, had been intermittently treated with disulfiram for nearly a decade; on several occasions, he had stopped taking disulfiram and resumed his alcohol use. When he first began taking disulfiram 9 years earlier, he had a toxic reaction after "testing" the medication by drinking alcohol. More recently, Mr. A was admitted to the hospital after drinking several glasses of wine following his daily disulfiram dose (in what appears to have been a suicidal gesture).

What Is Disulfiram and How Does It Work?

Disulfiram (Antabuse) facilitates alcohol abstinence by causing an adverse physical reaction when alcohol is consumed. It irreversibly inhibits aldehyde dehydrogenase (the enzyme that converts the relatively toxic metabolite acetaldehyde to the benign metabolite acetate); this enzyme is necessary for the metabolism of ethanol. Ingestion of a single dose begins to affect ethanol metabolism within 1 to 2 hours; its peak effects are seen at 12 hours, and its sustained effects (usually 12–72 hours) depend on the rate of new enzyme synthesis. In some individuals, the effects of a single dose can last up to 2 weeks.

If ethanol is ingested while taking disulfiram, the inhibition of aldehyde dehydrogenase causes increased levels of acetaldehyde; this results in a toxic reaction. Symptoms include throbbing headache, flushing, dizziness, vomiting, and blurred vision. In addition, significant cardiovascular effects (e.g., chest pain, palpitations, tachycardia, and hypotension) can occur. Severe reactions (which arise when disulfiram is used at very high doses or in individuals with cardiovascular disease) can include myocardial infarction, arrhythmia, congestive heart failure (CHF), or death. Serious clinical sequelae of disulfiram-ethanol reactions (e.g., shock, hypotension, or myocardial ischemia) should be managed aggressively; there is no specific antidote to the disulfiram-ethanol reaction.

What Is the Usual Dose of Disulfiram? What Are Its Side Effects? How Are Patients on Disulfiram Monitored?

The usual dose of disulfiram is 250 mg/day. Doses less than this tend not to produce aversive reactions with alcohol ingestion, while doses

Table 1. Selected Drug-Drug Interactions With Disulfiram

Medication	Interaction With Disulfiram	Potential Clinical Effect
Phenytoin	Decreased phenytoin metabolism	Symptoms of phenytoin toxicity: ataxia, tremor, confusion, nystagmus
Warfarin	Decreased warfarin metabolism	Increased bleeding susceptibility
Isoniazid	Inhibition of dopaminergic metabolic pathways	Incoordination, irritability, confusion
Benzodiazepines	Decreased benzodiazepine metabolism	Oversedation, confusion, ataxia
Metronidazole	Unknown CNS interaction	Paranoia, confusion
Imipramine/desipramine	Decreased hepatic metabolism	Symptoms of TCA toxicity: anticholinergic effects, sedation, orthostasis
Amitriptyline	Decreased hepatic metabolism (possibly resulting in elevated levels of dopamine or other neurotransmitters)	Psychosis, confusion

greater than (or equal to) 500 mg/day are associated with higher rates of problematic side effects (e.g., psychosis, hypertension, and hepatitis). Common side effects include gastrointestinal side effects (such as nausea and dyspepsia), mild sedation, and a metallic or garlic taste.

Disulfiram can cause hepatitis (usually dose-related and quite rare at 250 mg/day); therefore, liver function tests (LFTs) should be checked prior to starting treatment (most practitioners consider it acceptable to initiate treatment with disulfiram if the LFTs are less than twice the upper limit of the normal value). LFTs should be checked every 2 to 3 weeks for the first 2 months, then roughly every 3 months while disulfiram therapy continues. In the literature, there are no clear guidelines about treating patients with early cirrhosis. In general, we treat patients with early cirrhosis if their LFTs fall within the criteria we specify; if patients have LFTs that are elevated beyond these criteria or have portal hypertension, we avoid disulfiram use.

Disulfiram also interacts in a significant fashion with other drugs; it inhibits the biotransformation of warfarin, phenytoin, isoniazid, some benzodiazepines (e.g., diazepam), and tricyclic antidepressants (TCAs) (e.g., desipramine and imipramine). Therefore, prothrombin time (PT) should be monitored in patients taking warfarin, and levels of phenytoin and TCAs should be monitored if patients are taking these medications in combination with disulfiram (Table 1).

Does Disulfiram Work?

Disulfiram works modestly at best. As a long-term, unsupervised, outpatient monotherapy, disulfiram appears to be no better than placebo. The largest study of Veterans Administration (VA) patients by Fuller and coworkers[1] found that a small subset of patients (usually older and with strong social support) received some benefit from disulfiram therapy, but the group as a whole gained no long-term benefit in the achievement of alcohol abstinence. Programs in which disulfiram has been administered in a supervised setting have shown modest benefit in the achievement of abstinence, especially when this treatment has been part of a more comprehensive treatment program.

Who Should Not Receive Disulfiram Therapy?

As with all medications, the risks of treatment must be balanced against the risks of no treatment (in this case, the health risks of continued, untreated alcohol use). Disulfiram is relatively contraindicated when one of several conditions or medications is present. Hypotension and other cardiovascular effects associated with an ethanol-disulfiram reaction can occur. Therefore, patients with coronary artery disease (CAD), chronic cardiac arrhythmias, cardiomyopathy with CHF, chronic renal failure, cerebrovascular disease, and severe pulmonary disease should, in most cases, not take disulfiram. Furthermore, disulfiram use is contraindicated in pregnancy (because its use is associated with birth defects). Disulfiram can also exacerbate peripheral neuropathy and psychosis, and it can lower seizure threshold.

Furthermore, individuals who are unable to understand the consequences of using a substance that adversely reacts with disulfiram (e.g., patients with limited intelligence or with an organic brain syndrome) should not be prescribed disulfiram. Finally, patients should not receive disulfiram if they have a history of an adverse neurologic, psychiatric, or cardiovascular reaction to disulfiram. Disulfiram should also be avoided in patients with a history of dangerous impulsive behavior or significant suicidality.

What Other Medications Can Be Used in the Treatment of Alcoholism?

Naltrexone is frequently used in the treatment of alcohol disorders. Naltrexone is an opioid receptor antagonist that blocks the effects of endogenous opioids released through ethanol ingestion. It appears to reduce the risk of relapse to heavy drinking and the frequency of drinking compared to placebo. It does not have an aversive effect, but instead appears to decrease ethanol craving and the euphoria associated with ethanol ingestion. Therefore, because it does not cause a toxic reaction, it does not

decrease the rate of "slips" (brief relapses into alcohol consumption). However, its opioid-blocking effects do decrease problem drinking.

Two initial placebo-controlled trials[2,3] found that naltrexone increased abstinence from alcohol, decreased drinking days, and reduced alcohol craving among patients with alcohol dependence. Follow-up studies have been somewhat mixed, including a recent study[4] of 627 veterans with severe, chronic alcohol dependence that found no beneficial effect from naltrexone at 1 year. In most studies, naltrexone is effective in reducing drinking days and craving in compliant patients; the greatest difficulty has been ensuring treatment compliance.[5] Therefore, our experience suggests that naltrexone is most effective in patients with family or social support for their abstinence, or those in alcohol treatment programs.

Naltrexone is administered once per day; the usual dose is 50 mg/day. Side effects can include nausea (the most common side effect), dizziness, headache, fatigue, and insomnia. To reduce discontinuation due to initial side effects, some clinicians prescribe 25 mg for the first 3 to 4 days of treatment, then increase the daily dose to 50 mg. With use of naltrexone, LFTs should be followed because of potential hepatotoxicity (quite rare at the usual dose of 50 mg/day). Guidelines for LFT-monitoring are similar to those for disulfiram: LFTs should be checked every 2 to 3 weeks for the first 2 months of treatment, then roughly every 3 months during continuation treatment with naltrexone. Because of its irreversible blockade of opioid receptors, naltrexone should never be administered to an opioid-dependent patient, since it can cause an abstinence syndrome that lasts upwards of 72 hours. For this reason, naltrexone should not be prescribed for any patient who has used opioid medications in the last 7 to 10 days. In addition, many authors advise that coadministration of disulfiram and naltrexone should generally be avoided because of the potential hepatotoxicity of both medications.

Acamprosate (currently available only in Europe) is a third medication used in the treatment of alcohol disorders. It acts at both NMDA (glutaminergic) and GABA receptors to normalize the glutamatergic excitation associated with alcohol withdrawal and with early abstinence. It also appears to reduce the frequency of drinking when compared to use of placebo. Diarrhea is the most common side effect; no LFT-monitoring is required. Both naltrexone and acamprosate appear to have fewer drug-drug interactions and toxicity than disulfiram.

Should This Patient (Mr. A) Take Disulfiram?

No. The reasons for this are as follows:

1. Mr. A has used alcohol and disulfiram together twice (once in a passively suicidal way).
2. Safer and more effective treatments than disulfiram exist for alcohol dependence.
3. Disulfiram has not been particularly effective in the treatment of Mr. A's alcohol dependence.
4. Mr. A is elderly and likely has some cardiovascular disease that places him at greater risk for adverse consequences of a toxic reaction.

Mr. A's alcoholism can be addressed by utilizing a number of treatments. These include psychosocial interventions (e.g., Alcohol Anonymous [AA], Rational Recovery, outpatient substance abuse counseling, and residential programs), practical strategies to avoid relapse (e.g., removing alcohol from the home, avoiding triggering persons and locations, and support from sober friends or sponsors), use of other medications specifically for the treatment of alcohol dependence (e.g., naltrexone), and concomitant treatment of comorbid psychiatric conditions (e.g., depression). These treatments should be used in combination to give Mr. A the best chance of persistent abstinence and an improved long-term quality of life.

Drug names: desipramine (Norpramin and others), diazepam (Valium and others), disulfiram (Antabuse), imipramine, (Tofranil and others), isoniazid (Rifamate and others), naltrexone (ReVia), phenytoin (Dilantin and others), warfarin (Coumadin and others).

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Review Articles

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—A comprehensive review of disulfiram. The article describes the pharmacology, dosing, side effects, and toxicity of this medication. In addition, it reviews treatment studies of disulfiram and makes recommendations about its optimal clinical use.

Saitz R, O'Malley S. Pharmacotherapies for alcohol abuse. Med Clin N Am 1997;81:881–907
—A clear, concise, and comprehensive review of disulfiram and naltrexone. The article also discusses the use of antidepressants in patients with alcohol disorders and contains a brief section on acamprosate.

Hughes JC, Cook CC. The efficacy of disulfiram: a review of outcome studies. Addiction 1997;92:381–395
—A review of 38 outcome studies of disulfiram completed between 1967 and 1995. The authors found that use of oral disulfiram modestly decreased the quantity of alcohol use and the number of drinking days. However, disulfiram had little effect on the development of alcohol abstinence.

Swift RM. Drug therapy for alcohol dependence. N Engl J Med 1999;340:1482–1490
—A short, well-written article that broadly covers the topic. Along with descriptions of disulfiram, naltrexone, and acamprosate, the article includes discussions of other medications that may have potential benefit in patients with alcohol dependence. The article ends with treatment recommendations.

O'Malley SS, Krishnan-Sarin S, Rounsaville BJ. Naltrexone. In: Sadock BJ, Sadock VA, eds. Kaplan and Sadock's Comprehensive Textbook of Psychiatry, 7th ed. Philadelphia, Pa: Lippincott Williams and Wilkins; 2000:2407–2411
—A complete discussion of naltrexone. Pharmacologic properties, clinical indications, adverse effects, drug interactions, and dosing recommendations are all clearly and succinctly outlined. The authors list both cross-references within the textbook and external references for further information.

Fiellin DA, Reid MC, O'Connor PG. New therapies for alcohol problems: application to primary care. Am J Med 2000;108:227–237
—A practical and complete guide to the variety of treatments for problem alcohol use. The authors discuss both medication and psychosocial interventions, and they outline the evidence that supports each type of intervention. This review largely focuses on the application of these treatments in the primary care setting.

Anton RF. Pharmacologic approaches to the management of alcoholism. J Clin Psychiatry 2001;62(suppl 20):11–17
—A brief, well-written discussion of the topic. The author first outlines pertinent neurotransmitter physiology involved in alcohol dependence and discusses how the available treatments are linked to this physiology. The article then discusses clinical studies, side effects, and contraindications for disulfiram, naltrexone, and acamprosate. Treatment recommendations for each drug are made.

Original Articles

Fuller RK, Branchey L, Brightwell DR, et al. Disulfiram treatment of alcoholism: a Veterans Administration cooperative study. JAMA 1986;256:1449–1455
—This article describes a multicenter trial of disulfiram use for alcohol dependence. Six hundred five men were randomized to 1 of 3 groups (disulfiram [250 mg], disulfiram [1 mg], or no disulfiram) and were followed for 1 year. Those who received 250 mg of disulfiram had significantly fewer drinking days than did those in the other groups. However, no significant differences were detected among the groups in total abstinence, time to first drink, employment, or social stability.

Branchey L, Davis W, Lee WW, et al. Psychiatric complications of disulfiram treatment. Am J Psychiatry 1987;144:1310–1312
—This study investigated the possibility of psychiatric complications of disulfiram use in 605 alcoholic patients. The subjects were separated into 3 groups: those receiving disulfiram (250 mg), disulfiram (1 mg), or no disulfiram. The authors found no significant differences in the rate of psychiatric complications among the 3 groups. They suggested that a low rate of psychiatric complications resulted from disulfiram use.

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—A thoughtful article that discusses 3 patients who developed catatonia-like symptoms while taking disulfiram. In each case, the patient's symptoms included immobility, mutism, staring, and unresponsiveness. The author discusses possible mechanisms of the catatonia-like state, concluding that disulfiram's inhibition of dopamine conversion to norepinephrine potentially plays a role.

Volpicelli JR, Alterman AI, Hayashida M, et al. Naltrexone in the treatment of alcohol dependence. Arch Gen Psychiatry 1992;49:876–880
—A double-blind placebo-controlled trial of naltrexone in the treatment of 70 patients with alcohol dependence. Subjects were given naltrexone (50 mg/day) or placebo as an adjunct to treatment following alcohol detoxification. The authors found that naltrexone significantly reduced relapse, drinking days, and alcohol craving. This study found naltrexone to be well-tolerated.

Saxon AJ, Sloan KL, Reoux J, et al. Disulfiram use in patients with abnormal liver function test results. J Clin Psychiatry 1998;59:313–316
—This study examined the use of disulfiram in 57 patients with mildly elevated LFT results (transaminases < 200 and total bilirubin < 2) and/or hepatitis C. They found that 5 of 18 patients with elevated ALT levels at baseline had significant elevations of LFTs when disulfiram was added, though in all but one patient, the levels of transaminases appeared to plateau during disulfiram treatment. No other patients in the study had marked elevations of transaminases. This study indicated that patients with mildly elevated LFTs or hepatitis C can be treated with disulfiram, but that LFT-monitoring is necessary in such patients.

Krystal JH, Cramer JA, Krol WF, et al. Naltrexone in the treatment of alcohol dependence. N Engl J Med 2001;345:1734–1739
—A multicenter, double-blind, placebo-controlled trial of 627 veterans (virtually all men) with chronic and severe alcohol dependence. The subjects were randomly assigned to 1 of 3 treatments: 12 months of naltrexone (50 mg/day), 12 months of placebo, or 3 months of naltrexone followed by 9 months of placebo. The authors found no significant between-group differences in days to relapse, drinking days, or number of drinks per day, suggesting that naltrexone may not be effective for men with chronic and severe alcohol dependence.