

# Pharmacotherapy of alcohol dependence

## How and when to use disulfiram and naltrexone

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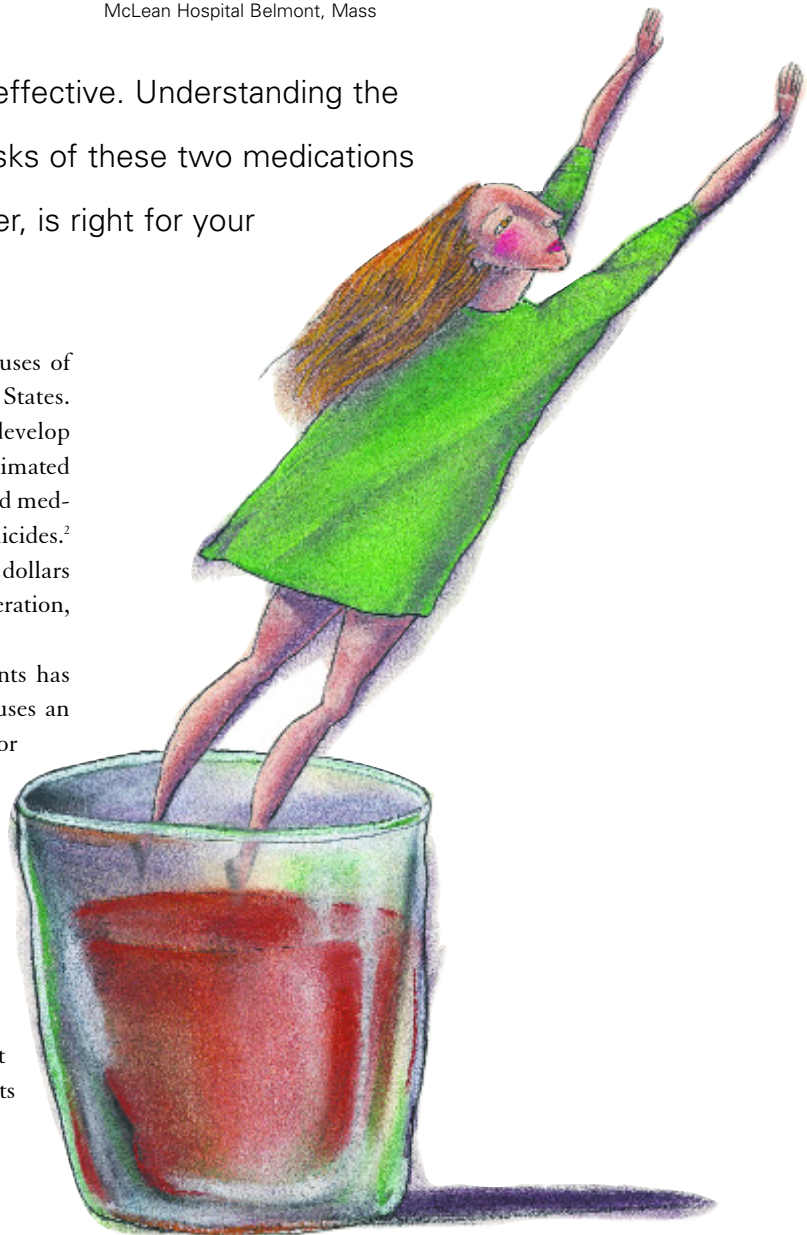
Both agents have been shown to be effective. Understanding the mechanism of action, benefits, and risks of these two medications can help you determine which, if either, is right for your patient with alcohol problems.

**A**lcohol dependence is one of the leading causes of morbidity and mortality in the United States. Approximately 10% of Americans will develop alcoholism at some point in their lives,<sup>1</sup> and an estimated 100,000 individuals die each year due to alcohol-related medical complications, automobile accidents, and homicides.<sup>2</sup> Alcohol dependence also costs the U.S. billions of dollars annually in health care costs, lost productivity, incarceration, and property destruction.

The search for effective pharmacologic treatments has long been a focus of research. Disulfiram, which causes an aversive reaction when combined with alcohol, was for many years the only medication in use. More recently, the opiate antagonist naltrexone has also been used to treat alcohol-dependent patients.

The homotaurine derivative, acamprosate, has recently shown great promise. Though used widely in Europe,<sup>3</sup> it is not approved for use in this country.

This article will therefore focus on disulfiram and naltrexone: their pharmacology, efficacy, side effects, and dosing strategies. We also will present guidelines for discussing each medication with patients and for deciding which, if either, to prescribe.



### Differences in pharmacology

**Disulfiram** Since the serendipitous discovery of its reactive property with alcohol in the 1940s, disulfiram has been used in the pharmacological treatment of alcoholism. The agent disrupts alcohol metabolism by inhibiting the action of aldehyde dehydrogenase, thus blocking the conversion of acetaldehyde to acetate. Accumulation of acetaldehyde, the first metabolite of ethanol, causes numerous unpleasant effects, including flushing, weakness, and nausea.<sup>4</sup> In addition to acting on aldehyde dehydrogenase, disulfiram inhibits dopamine- $\beta$ -hydroxylase.<sup>5</sup>

Disulfiram is absorbed from the gastrointestinal tract and is rapidly distributed to tissues and organs. It begins to affect alcohol metabolism within 1 to 2 hours, with a peak at 12 hours. It is slowly excreted from the body over the next 2 weeks, although its effects may be lost sooner as the body secretes new enzyme.<sup>4</sup>

The ethanol-disulfiram reaction is characterized by flushing, throbbing in the head and neck, respiratory difficulty, vomiting, sweating, thirst, weakness, and hypotension (*Table 1*). In some cases, the reaction can be fatal.

**Naltrexone** Following its approval for use in treating opioid dependence in the mid-1980s, the opiate antagonist naltrexone was approved nearly a decade ago for use in treating individuals with alcohol dependence. Research interest in the use of naltrexone for this purpose grew from theories that the endogenous opiate system may be involved in the development of alcohol dependence.<sup>6</sup> Two simultaneously published studies in 1992 showed the benefit of naltrexone in alcohol dependence;<sup>7-8</sup> this led to its approval by the Food and Drug Administration.

Naltrexone is metabolized to its major metabolite, 6- $\beta$ -naltrexol, and is then excreted in the urine as both the original compound and this metabolite.<sup>9</sup> The half-life of naltrexone in chronic administration is approximately 10 hours; the half-life of 6- $\beta$ -naltrexol is 12 to 16 hours.

### Comparison of efficacy

**Disulfiram** Results concerning efficacy have been mixed. Initial studies showed promising effects but were limited to anecdotal evidence and case studies. More recent studies have addressed issues relating to proper control groups, compliance, and motivation in evaluating disulfiram's effect on alcohol consumption. Early studies used

placebo groups to control for the effects of counseling or regular medical monitoring. However, no controls were employed to distinguish between the psychological effects of disulfiram (e.g., fear of a reaction) and its pharmacologic effects.

Fuller and Roth<sup>10</sup> addressed this concern by designing a double-blind study that consisted of 3 groups. Group 1 received disulfiram 250 mg/d, group 2 received 1 mg/d (a pharmacologically ineffective dose), and group 3 received a placebo. Importantly, patients in both groups 1 and 2 were informed that they were receiving disulfiram and were

Table 1

### SYMPTOMS OF AN ETHANOL-DISULFIRAM REACTION

- Flushing
- Throbbing in head and neck
- Respiratory difficulty
- Vomiting
- Sweating
- Thirst
- Weakness
- Hypotension

The intensity of the reaction is generally related to the amount of alcohol and disulfiram consumed. Because even small amounts of alcohol may cause a reaction, individuals taking disulfiram should avoid all forms of alcohol, including certain mouthwashes and cough syrups. Patients also should be instructed to read the ingredients of foods and medications they consume.

While the recommended daily dose for disulfiram ranges from 125 mg to 500 mg, individuals can vary widely in their reactions. Dosages below 250 mg/d have failed to produce aversive reactions in some individuals who drink alcohol. Dosages of 250 mg/d or higher, however, may cause toxic side effects, including a more severe reaction with alcohol. Clinicians should be aware that in a few patients, the dosage needed to produce an aversive reaction may be higher than the dosage that produces toxicity.<sup>4</sup>

The authors generally prescribe 125 mg/d, which is at the low end of the usual dose range, since the fear of a reaction—not the reaction itself—is the major therapeutic action of disulfiram. Moreover, a lower dosage diminishes (but by no means eliminates) the likelihood of a highly dangerous alcohol-disulfiram reaction.

warned of a possible ethanol-disulfiram reaction. At a 6-month follow-up, patients receiving disulfiram showed a small but significant increase in abstinence compared with those receiving placebo. Interestingly, there was no difference between patients receiving 250 mg of disulfiram and those receiving the ineffective 1 mg dose, suggesting that the primary action of disulfiram is the fear of a reaction with alcohol, not the agent's pharmacologic effects.

A number of studies have shown that patients who agree to take disulfiram and continue taking it are generally highly motivated; such patients unsurprisingly experience better treatment outcomes.

In the largest controlled, blinded study of disulfiram performed to date, Fuller et al<sup>11</sup> evaluated disulfiram treatment in 605 male veterans randomly assigned to disulfiram 250 mg a day, disulfiram 1 mg a day, or placebo. No significant differences were found between groups in total abstinence or time to first drink. Among patients who participated in all assessments and who drank at least once during the study, however, those receiving 250 mg had fewer drinking days than those in either control group.

The authors concluded that disulfiram may help reduce drinking frequency after a return to drinking, but does not contribute to continuous abstinence or to delay in time to first drink. Notably, despite a medication compliance rate of only 20%, a significant relationship existed between medication compliance and complete abstinence, regardless of treatment group. O'Farrell and colleagues<sup>14</sup> have studied ways to increase compliance with disulfiram, developing the concept of the "Antabuse contract," in which the patient takes disulfiram in front of a significant other as part of a couple's therapy program.

How long should a patient continue taking disulfiram? Unfortunately, the ideal length of disulfiram treatment has not been established. While most randomized trials only administer disulfiram for a few months, research by Ojehagen et al<sup>15</sup> has shown that long-term treatment (greater than 12 months) with disulfiram is significantly related to positive drinking outcomes during the 2 years following treatment.

Several studies have shown that patients who agree to take disulfiram and continue taking it experience better outcomes



**Naltrexone** The two initial landmark studies of naltrexone for alcohol dependence were published nearly a decade ago. Volpicelli et al<sup>7</sup> conducted a double-blind, placebo-controlled trial of naltrexone 50 mg/d for 12 weeks with 70 male veterans who also received intensive psychosocial alcohol rehabilitation. Study participants who received naltrexone had fewer drinking days, less craving for alcohol, and a lower rate of full-blown relapse than did patients who received placebo. The major effect of naltrexone occurred among patients who sampled alcohol; only half of those on naltrexone progressed from first drink to a full-blown relapse, compared to a 95% rate of relapse among those who initiated drinking while receiving placebo.

O'Malley et al<sup>8</sup> also found naltrexone to be more effective than placebo and found an interesting interaction with psychosocial treatment. Individuals who received weekly abstinence-oriented supportive therapy were more likely to be continuously abstinent from alcohol at the end of the 12-week study period. Those who received naltrexone along with cognitive behavioral coping skills therapy were least likely to progress to a full-blown relapse if they did drink.

More recently, Anton et al<sup>12</sup> conducted a double-blind, placebo-controlled trial of naltrexone in 131 patients, all of whom received cognitive behavioral therapy (CBT). Those receiving naltrexone had a significantly longer period prior to relapse, fewer drinking days, and fewer drinks per drinking day than the placebo group. No significant differences were reported between the groups in time prior to the first drink.

These studies suggest that naltrexone may diminish the likelihood of progression from first drink to full-blown relapse. This may occur through the agent's attenuation of the reinforcing effects of alcohol.<sup>13</sup> While naltrexone does not fully block alcohol the way it blocks opioid drugs, the reduction in alcohol's positive effects may help naltrexone responders to contain their "slips" and prevent progression to a full-blown relapse.

### The difference in adverse effects

**Disulfiram** Adverse effects (see *Table 2*) arise from 3 main causes:

1. Medical complications during an ethanol-disulfiram reaction;

Table 2

## HOW DISULFIRAM, NALTREXONE WORK

	Disulfiram	Naltrexone
<b>Mechanism of action</b>	Interrupts metabolism of alcohol, leads to a buildup of acetaldehyde	Opiate antagonist, may attenuate reinforcing property of alcohol
<b>Recommended dose*</b>	25-500 mg	50 mg
<b>Side effects and adverse events</b>	Drowsiness, impotence, headache, acne, metallic aftertaste, hepatitis, neuritis, ethanol-disulfiram reaction	Nausea, vomiting, headache, anxiety, dizziness, fatigue, insomnia, elevated liver enzymes

\*Physicians Desk Reference 55<sup>th</sup> ed. Montvale, NJ: Medical Economics, 2001

- Toxicity due to disulfiram or its metabolites;
- Interactions between disulfiram and other medications.

Medical complications arising from an ethanol-disulfiram reaction can include tachycardia, hypotension, and electrocardiographic changes. Fatalities have been reported due to myocardial infarction or cerebrovascular accident.<sup>5</sup> As a result, people with a history of severe myocardial disease should generally not be prescribed disulfiram.

Side effects from disulfiram itself include drowsiness, impotence, headache, acne, and a metallic or garlic-like aftertaste. Toxicity can also lead to psychiatric reactions such as increased depression and psychosis, possibly because of the inhibition of dopamine  $\beta$ -hydroxylase.<sup>5</sup>

Hepatic and neurological reactions are the most commonly reported toxic reactions.<sup>19</sup> Disulfiram-induced hepatitis usually occurs within 2 months of initiation of treatment, but may occur up to 6 months after starting disulfiram.<sup>20</sup> This form of liver toxicity is believed to be an allergic or hypersensitivity reaction and can lead to hepatic necrosis and death due to liver failure. Some clinicians recommend obtaining liver function tests at regular intervals (e.g., at baseline, 2 weeks, 4 weeks, then monthly for 6 months), although the optimal frequency of testing after

week 2 is not well established.

Neurological reactions make up approximately 20% of the overall reported side effects from disulfiram, with the most frequent diagnosis being polyneuropathy. Other important reported adverse neurological effects include optic and peripheral neuritis.<sup>19</sup>

Disulfiram interacts with a number of medications, primarily by slowing down their metabolism and thus increasing risk of toxicity. These drugs include phenytoin, theophylline, anticoagulant drugs, isoniazid, and amitriptyline.<sup>19</sup> Prior to starting treatment with disulfiram, phenytoin serum levels should be obtained and monitored throughout treatment. Dosage of oral anticoagulant drugs such as warfarin should also be monitored carefully.

**Naltrexone** The most common side effect is nausea, which typically occurs in the first week of treatment. In the largest study of naltrexone published to date, approximately 10% of naltrexone-treated subjects reported this side effect.<sup>16</sup> Other side effects include headache, anxiety, dizziness, fatigue, vomiting, and insomnia.<sup>16</sup>

Elevated liver enzymes have been reported with use,<sup>17</sup> so liver function should be monitored in patients receiving this medication.

It is unclear how often liver function tests should be performed. One text<sup>18</sup> recommends baseline assessment of liver function, monthly monitoring for 3 months, then testing every 2 to 6 months afterwards if results are normal.

### Other clinical considerations

**Disulfiram** Individuals with a history of allergy to thiuram derivatives used in rubber vulcanization or pesticides should not be given disulfiram. Caution should also be used with patients suffering from myocardial disease, diabetes mellitus, cirrhosis, hypothyroidism, seizure disorder, or impaired renal function. Finally, patients should not take disulfiram unless they have abstained

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from alcohol for at least 12 hours.

**Naltrexone** Although the recommended dosage of naltrexone for alcohol dependence is 50 mg/d, some patients who experience side effects at that dosage may tolerate 25 mg/d, so starting at this lower dose is often advisable. Some researchers are analyzing the effects of higher dosages (e.g., 100 mg/d) because of evidence that higher blood levels of 6- $\beta$ -naltrexol might improve treatment outcome.<sup>9</sup> The optimal dosage of naltrexone for alcohol dependence is currently not settled, however, and may vary among patients.

Patients should be free of opiates for at least 7 days prior to initiating naltrexone; in the case of methadone, a 10- to 14-day opiate-free interval is prudent. Clinicians should wait approximately 4 days after the patient's last drink before initiating therapy, since starting naltrexone earlier may lead to more side effects.

### Educating patients about both agents

**Disulfiram** This medication is not to be prescribed lightly; only patients who are fully aware of its potential risks should be taking it. Patients need to be both *willing* and *able* to avoid alcohol both in beverage and disguised forms (e.g., alcohol-laced cough syrups).

One useful question to ask patients is, "Can you imagine yourself drinking on disulfiram?" Patients who admit that disulfiram would not deter them from drinking, or who cannot commit to avoiding alcohol in any form, should not use this medication.

**Naltrexone** Some alcohol-dependent patients are interested in taking naltrexone because they have heard that it may diminish the likelihood of progression from initial drink to full-blown relapse, thus helping them to become controlled drinkers.

Bear in mind that naltrexone does *not* convert alcohol-dependent individuals into controlled drinkers. Rather, you should tell patients that naltrexone may help them return to abstinence more quickly in the event that they do slip. This statement is consistent with the data about naltrexone and helps to establish and reinforce the goal of abstinence for alcohol-dependent patients.

Some patients believe that naltrexone will help them to become controlled drinkers. This is not the case

### Which medication for which patient?

When considering which, if either, medication to prescribe for an alcohol-dependent patient, you should initially determine whether contraindications exist. (A rubber allergy would preclude disulfiram, for example.) Then obtain a medical evaluation, including liver function tests, prior to initiating either medication.

While the guidelines for adequate liver function to initiate these medications is a matter of controversy, some clinicians recommend that liver enzymes should be twice the upper limit of normal or better, and that the medications should be stopped if liver function tests are 3 times the upper limit of normal or worse. Some clinicians use more liberal or conservative guidelines, although most recommend that an elevated bilirubin contraindicates the use of either agent.

Assuming that the patient is medically able to take either one, tell the patient that there are 2 medications approved for the treatment of alcohol dependence, and briefly describe each. Then ask the patient if he or she is potentially interested in either. Many patients will opt for no pharmacotherapy, some for naltrexone, and a smaller portion for disulfiram. This choice may vary over time, however, based on the patient's clinical status. By remaining flexible and sharing this decision-making process with the patient, you increase

By integrating pharmacologic and psychosocial treatments for alcohol dependence, clinicians can improve outcomes for patients with this life-threatening disease. Disulfiram is designed to deter drinking because of the aversive reaction that occurs when it is combined with alcohol. Naltrexone, an opiate antagonist, may decrease patients' cravings for alcohol, and may diminish the likelihood of full-blown relapse in patients who do initiate drinking.

the likelihood of medication compliance.

Current evidence suggests that both disulfiram and naltrexone are effective only in conjunction with alcohol-focused psychosocial treatment; this may include professional alcoholism treatment, support groups such as Alcoholics Anonymous, or, ideally, a combination of the two.

Monitoring compliance and side effects is also critical. By integrating pharmacologic and psychosocial approaches for alcohol-dependent patients, outcomes can be improved for this prevalent and highly treatable population.

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**Related resources**

- ▶ The National Institute on Alcohol Abuse and Alcoholism (NIAAA) [www.niaaa.nih.gov](http://www.niaaa.nih.gov)
- ▶ American Academy of Addiction Psychiatry (AAAP) [www.aaap.org](http://www.aaap.org)
- ▶ American Society of Addiction Medicine (ASAM) [www.asam.org](http://www.asam.org)

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**DRUG BRAND NAMES**

Acamprosate • Campral	Naltrexone • ReVia
Disulfiram • Antabuse	Warfarin • Coumadin, Miradon
Isoniazid • Laniazid, Nidrazid	

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**DISCLOSURE**

The authors report no financial relationship with any company whose products are mentioned in this article.

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