Excerpt from

Helping Patients Who Drink Too Much: A Clinician's Guide

U.S. Department of Health and Human Services
National Institutes of Health
National Institute on Alcohol Abuse and Alcoholism
NIH Publication 07–3769
www.niaaa.nih.gov/guide
October 2008 Update

Prescribing Medications for Alcohol Dependence

Three oral medications (naltrexone, acamprosate, and disulfiram) and one injectable medication (extended-release injectable naltrexone) are currently approved for treating alcohol dependence. Topiramate, an oral medication used to treat epilepsy and migraine, has recently been shown to be effective in treating alcohol dependence, although it is not approved by the FDA for this indication. All of these medications have been shown to help patients reduce drinking, avoid relapse to heavy drinking, achieve and maintain abstinence, or gain a combination of these effects. As is true in treating any chronic illness, addressing patient adherence systematically will maximize the effectiveness of these medications (see "Supporting Patients Who Take Medications for Alcohol Dependence," page 5).

When should medications be considered for treating an alcohol use disorder?

The drugs noted above have been shown to be effective adjuncts to the treatment of alcohol dependence. Thus, consider adding a medication whenever you're treating someone with active alcohol dependence or someone who has stopped drinking in the past few months but is experiencing problems such as craving or "slips." Patients who previously failed to respond to psychosocial approaches alone are particularly strong candidates for medication treatment.

Must patients agree to abstain?

No matter which alcohol dependence medication is used, patients who have a goal of abstinence, or who can abstain even for a few days prior to starting the medication, are likely to have better outcomes. Still, it's best to determine individual goals with each patient. Some patients may not be willing to endorse abstinence as a goal, especially at first. If a patient with alcohol dependence agrees to reduce drinking substantially, it's best to engage him or her in that goal while continuing to note that abstinence remains the optimal outcome.

A patient's willingness to abstain has important implications for the choice of medication. Most studies on effectiveness have required patients to abstain before starting treatment. A notable exception is topiramate, which was prescribed to study volunteers

who were still drinking.[1] Both oral and extended-release injection naltrexone also may be helpful in reducing heavy drinking and encouraging abstinence in patients who are still drinking.[2,3] However, its efficacy is much higher in patients who can abstain for 4 to 7 days before initiating treatment. Acamprosate, too, is only approved for use in patients who are abstinent at the start of treatment, and patients should be fully withdrawn before starting. Disulfiram is contraindicated in patients who wish to continue to drink, because a disulfiram–alcohol reaction occurs with any alcohol intake at all.

Which of the medications should be prescribed?

Which medication to use will depend on clinical judgment and patient preference. Each has a different mechanism of action. Some patients may respond better to one type of medication than another. (See chart on pages 8–9 for prescribing information.)

- ### Naltrexone

  Mechanism: Naltrexone blocks opioid receptors that are involved in the rewarding effects of drinking alcohol and the craving for alcohol. It's available in two forms: oral (Depade®, ReVia®), with once-daily dosing, and extended-release injectable (Vivitrol®), given as once-monthly injections.

  Efficacy: Oral naltrexone reduces relapse to heavy drinking, defined as 4 or more drinks per day for women and 5 or more for men.[4,5] It cuts the relapse risk during the first 3 months by about 36 percent (about 28 percent of patients taking naltrexone relapse versus about 43 percent of those taking a placebo).[5] Thus, it is especially helpful for curbing consumption in patients who have drinking "slips." It is less effective in maintaining abstinence.[4,5] In the single study available when this *Guide* update was published, extended-release injectable naltrexone resulted in a 25 percent reduction in the proportion of heavy drinking days compared with a placebo, with a higher rate of response in males and those with lead-in abstinence.[3]

- ### Topiramate

  Mechanism: The precise mechanism of action is unclear. Topiramate is thought to work by increasing inhibitory (GABA) neurotransmission and reducing stimulatory (glutamate) neurotransmission. It is available in oral form and requires a slow upward titration of dose to minimize side effects.

  Efficacy: Topiramate has been shown in two randomized controlled trials to significantly improve multiple drinking outcomes, compared with placebo.[1,6] Over the course of a 14-week trial, topiramate significantly increased the proportion of volunteers with 28 consecutive days of abstinence or non-heavy drinking.[1] In both studies, the differences between topiramate and placebo groups were still diverging at the end of the trial, suggesting that the maximum effect may not have been reached. The magnitude of topiramate's effect may be larger than that for naltrexone or acamprosate. Importantly, efficacy was established in volunteers who were drinking at the time of starting the medication.

- **Acamprosate**

  Mechanism: Acamprosate (Campral®) acts on the GABA and glutamate neurotransmitter systems and is thought to reduce symptoms of protracted abstinence such as insomnia, anxiety, restlessness, and dysphoria. It's available in oral form (three times daily dosing).

  Efficacy: Acamprosate increases the proportion of dependent drinkers who maintain abstinence for several weeks to months, a result demonstrated in multiple European studies and confirmed by a meta-analysis of 17 clinical trials.[7] The meta-analysis reported that 36 percent of patients taking acamprosate were continuously abstinent at 6 months, compared with 23 percent of those taking a placebo.

  More recently, two large U.S. trials failed to confirm the efficacy of acamprosate,[8,9] although secondary analyses in one of the studies suggested possible efficacy in patients who had a baseline goal of abstinence.[9] A reason for the discrepancy between European and U.S. findings may be that patients in European trials had more severe dependence than patients in U.S. trials,[7,8] a factor consistent with preclinical studies showing that acamprosate has a greater effect in animals with a prolonged history of dependence.[10] In addition, before starting medication, most patients in European trials had been abstinent longer than patients in U.S. trials.[11]

- **Disulfiram**

  Mechanism: Disulfiram (Antabuse®) interferes with degradation of alcohol, resulting in accumulation of acetaldehyde, which, in turn, produces a very unpleasant reaction including flushing, nausea, and palpitations if the patient drinks alcohol. It's available in oral form (once-daily dosing).

  Efficacy: The utility and effectiveness of disulfiram are considered limited because compliance is generally poor when patients are given it to take at their own discretion.[12] It is most effective when given in a monitored fashion, such as in a clinic or by a spouse.[13] (If a spouse or other family member is the monitor, instruct both monitor and patient that the monitor should simply observe the patient taking the medication and call you if the patient stops taking it for 2 days.) Some patients will respond to self-administered disulfiram, however, especially if they're highly motivated to abstain. Others may use it episodically for high-risk situations, such as social occasions where alcohol is present.

How long should medications be maintained?

The risk for relapse to alcohol dependence is very high in the first 6 to 12 months after initiating abstinence and gradually diminishes over several years. Therefore, a minimum initial period of 3 months of pharmacotherapy is recommended. Although an optimal

treatment duration hasn't been established, it is reasonable to continue treatment for a year or longer if the patient responds to medication during this time when the risk of relapse is highest. After patients discontinue medications, they may need to be followed more closely and have pharmacotherapy reinstated if relapse occurs.

If one medication doesn't work, should another be prescribed?

If there's no response to the first medication selected, you may wish to consider a second. This sequential approach appears to be common clinical practice, but currently there are no published studies examining its effectiveness. Similarly, there is not yet enough evidence to recommend a specific ordering of medications.

Is there any benefit to combining medications?

A large U.S. trial found no benefit to combining acamprosate and naltrexone.[8] Naltrexone, disulfiram, and both in combination were compared with placebo in the treatment of alcohol dependence in patients with coexisting Axis I psychiatric disorders.[14] Equivalently better outcomes were obtained with either medication, but combining them did not have any additional effect. At this time, there is no evidence supporting the combination of medications, but the number of studies examining this question is limited.

Should patients receiving medications also receive specialized alcohol counseling or a referral to mutual help groups?

Offering the full range of effective treatments will maximize patient choice and outcomes, as no single approach is universally successful or appealing to patients. The different approaches—medications for alcohol dependence, professional counseling, and mutual help groups—are complementary. They share the same goals while addressing different aspects of alcohol dependence: neurobiological, psychological, and social. The medications aren't prone to abuse, so they don't pose a conflict with other support strategies that emphasize abstinence.

Almost all studies of medications for alcohol dependence have included some type of counseling, and it's recommended that all patients taking these medications receive at least brief medical counseling. Evidence is accumulating that weekly or biweekly brief (i.e., 15–20 minutes) counseling by a health professional combined with prescribing a medication is an effective treatment for many patients during early recovery.[1,6,8,15] Medical counseling focuses on encouraging abstinence, adherence to the medication, and participation in community support groups. (For more information, see "Supporting Patients Who Take Medications for Alcohol Dependence" on page 5 and "Should I recommend any particular behavioral therapy for patients with alcohol use disorders?" in the full *Guide* on page 31.)

Supporting Patients Who Take Medications for Alcohol Dependence

Pharmacotherapy for alcohol dependence is most effective when combined with some behavioral support, but this doesn't need to be specialized, intensive alcohol counseling. Nurses and physicians in general medical and mental health settings, as well as counselors, can offer brief but effective behavioral support that promotes recovery. Applying this medication management approach in such settings would greatly expand access to effective treatment, given that many patients with alcohol dependence either don't have access to specialty treatment or refuse a referral.

How can general medical and mental health clinicians support patients who take medication for alcohol dependence?

Managing the care of patients who take medication for alcohol dependence is similar to other disease management strategies, such as initiating insulin therapy in patients with diabetes mellitus. In the recent Combining Medications and Behavioral Interventions (COMBINE) clinical trial, physicians, nurses, and other health care professionals in outpatient settings delivered a series of brief behavioral support sessions for patients taking medications for alcohol dependence.[8] The sessions promoted recovery by increasing adherence to the medication and supporting abstinence through education and referral to support groups.[8] (For a set of how-to templates outlining this program, see pages 19–22 in the full *Guide*.) It was designed for easy implementation in nonspecialty settings, in keeping with the national trend toward integrating the treatment of substance use disorders into medical practice.

What are the components of medication management support?

Medication management support consists of brief, structured outpatient sessions conducted by a health care professional. The initial session starts by reviewing with the patient the medical evaluation results as well as the negative consequences of drinking. This information frames a discussion about the diagnosis of alcohol dependence, the recommendation for abstinence, and the rationale for medication. The clinician then provides information on the medication itself and adherence strategies and encourages participation in a mutual support group such as Alcoholics Anonymous (AA).

In subsequent visits, the clinician assesses the patient's drinking, overall functioning, medication adherence, and any side effects from the medication. Session structure varies according to the patient's drinking status and treatment compliance, as outlined on page 22 in the full *Guide*. When a patient doesn't adhere to the medication regimen, it's important to evaluate the reasons and help the patient devise plans to address them. A helpful summary of strategies for handling nonadherence is provided in the "Medical Management Treatment Manual" from Project COMBINE, available online at www.niaaa.nih.gov/guide.

As conducted in the COMBINE trial, the program consisted of an initial session of about 45 minutes followed by eight 20-minute sessions during weeks 1, 2, 4, 6, 8, 10, 12, and 16. General medical or mental health practices may not follow this particular schedule, but it's offered along with the templates as a starting point for developing a program that works for your practice and your patients.

Can medication management support be used with patients who don't endorse a goal of abstinence?

This medication management program has been tested only in patients for whom abstinence was recommended, as is true with most pharmacotherapy studies. It's not known whether it would also work if the patient's goal is to cut back instead of abstain. Even when patients do endorse abstinence as a goal, they often cut back without quitting. You're encouraged to continue working with those patients who are working toward recovery but haven't yet met the optimal goals of abstinence or reduced drinking with full remission of dependence symptoms. You also may find many of the techniques used in medication management support—such as linking symptoms and laboratory results with heavy alcohol use—to be helpful for managing alcohol-dependent patients in general.

References

1. Johnson BA, Rosenthal N, Capece JA, et al. Topiramate for Alcoholism Advisory Board and the Topiramate for Alcoholism Study Group. Topiramate for treating alcohol dependence: A randomized controlled trial. *JAMA: The Journal of the American Medical Association.* 298(14):1641–1651, 2007.
2. Kranzler HR, Armeli S, Tennen H, et al. Targeted naltrexone for early problem drinkers. *J Clin Psychopharmacol.* 23(3):294–304, 2003.
3. Garbutt JC, Kranzler HR, O'Malley SS, et al. Efficacy and tolerability of long-acting injectable naltrexone for alcohol dependence: A randomized controlled trial. *JAMA: The Journal of the American Medical Association.* 293(13):1617–1625, 2005.
4. Bouza C, Angeles M, Munoz A, Amate JM. Efficacy and safety of naltrexone and acamprosate in the treatment of alcohol dependence: A systematic review. *Addiction.* 99(7):811–828, 2004.
5. Srisurapanont M, Jarusuraisin N. Naltrexone for the treatment of alcoholism: A meta-analysis of randomized controlled trials. *Int J Neuropsychopharmacol.* 8(2):267–280, 2005.
6. Johnson BA, Ait-Daoud N, Bowden C, et al. Oral topiramate for treatment of alcohol dependence: A randomised controlled trial. *The Lancet* 361(9370):1677–1685, 2003.
7. Mann K, Lehert P, Morgan MY. The efficacy of acamprosate in the maintenance of abstinence in alcohol-dependent individuals: Results of a metaanalysis. *Alcohol Clin Exp Res*. 28(1):51–63, 2004.
8. Anton RF, O'Malley SS, Ciraulo DA, et al., for the COMBINE Study Research Group. Combined pharmacotherapies and behavioral interventions for alcohol dependence: The COMBINE study: A randomized controlled trial. *JAMA: The Journal of the American Medical Association.* 295(17):2003–2017, 2006.

9. Mason BJ, Goodman AM, Chabac S, Lehert P. Effect of oral acamprosate on abstinence in patients with alcohol dependence in a double-blind, placebo-controlled trial: The role of patient motivation. *J Psychiatr Res*. 40(5):383–393, 2006.
10. Rimondini R, Arlinde C, Sommer W, Heilig M. Longlasting increase in voluntary ethanol consumption and transcriptional regulation in the rat brain after intermittent exposure to alcohol. *FASEB J*. 16(1):27–35, 2002.
11. Mason BJ, Ownby RL. Acamprosate for the treatment of alcohol dependence: A review of double-blind, placebo-controlled trials. *CNS Spectrums.* 5:58–69, 2000.
12. Fuller RK, Gordis E. Does disulfiram have a role in alcoholism treatment today? *Addiction.* 99(1):21–24, 2004
13. Allen JP, Litten RZ. Techniques to enhance compliance with disulfiram. *Alcohol Clin Exp Res*. 16(6):1035–1041, 1992.
14. Petrakis L, Poling L, Levinson C, et al., Naltrexone and disulfiram in patients with alcohol dependence and comorbid psychiatric disorders. *Biological Psychiatry.* 57(10):1128–1137, 2005.
15. O'Malley SS, Rounsaville BJ, Farren C., et al., Initial and maintenance naltrexone treatment for alcohol dependence using primary care vs. specialty care: A nested sequence of 3 randomized trials. *Archives of Internal Medicine.* 163(14):1695–1704, 2003.

Medications for Treating Alcohol Dependence

Updated October 2008

	Naltrexone (Depade®, ReVia®)	**Extended-release Injectable Naltrexone** (Vivitrol®)	**Acamprosate** (Campral®)	**Disulfiram** (Antabuse®)	**Topiramate** (Topamax®)
Action	Blocks opioid receptors, resulting in reduced craving and reduced reward in response to drinking.	Same as oral naltrexone; 30-day duration.	Affects glutamate and GABA neurotransmitter systems, but its alcohol-related action is unclear.	Inhibits intermediate metabolism of alcohol, causing a buildup of acetaldehyde and a reaction of flushing, sweating, nausea, and tachycardia if a patient drinks alcohol.	Thought to work by increasing inhibitory (GABA) neurotransmission and reducing stimulatory (glutamate) neurotransmission
Contraindications	Currently using opioids or in acute opioid withdrawal; anticipated need for opioid analgesics; acute hepatitis or liver failure.	Same as oral naltrexone, plus inadequate muscle mass for deep intramuscular injection; rash or infection at the injection site.	Severe renal impairment (CrCl ≤ 30 mL/min).	Concomitant use of alcohol or alcohol-containing preparations or metronidazole; coronary artery disease; severe myocardial disease; hypersensitivity to rubber (thiuram) derivatives.	Hypersensitivity to topiramate.
Precautions	Other hepatic disease; renal impairment; history of suicide attempts or depression. If opioid analgesia is needed, larger doses may be required and respiratory depression may be deeper and more prolonged. Pregnancy Category C. Advise patients to carry a wallet card to alert medical personnel in the event of an emergency. For wallet card information, see *www.niaaa.nih.gov/guide*.	Same as oral naltrexone, plus hemophilia or other bleeding problems.	Moderate renal impairment (dose adjustment for CrCl between 30 and 50 mL/min); depression or suicidal ideation and behavior. Pregnancy Category C.	Hepatic cirrhosis or insufficiency; cerebrovascular disease or cerebral damage; psychoses (current or history); diabetes mellitus; epilepsy; hypothyroidism; renal impairment. Pregnancy Category C. Advise patients to carry a wallet card to alert medical personnel in the event of an emergency. For wallet card information, see *www.niaaa.nih.gov/guide*.	Narrow angle glaucoma, kidney stones, renal or hepatic impairment, severely underweight, use of CNS depressants. Pregnancy Category C.
Serious adverse reactions	Will precipitate severe withdrawal if the patient is dependent on opioids; hepatotoxicity (although does not appear to be a hepatotoxin at the recommended doses).	Same as oral naltrexone, plus injection site reactions that may be severe (click here for FDA alert). Instruct patients to closely monitor site and seek care immediately if reaction is worsening. Also depression and rare events including allergic pneumonia and suicidal ideation and behavior.	Rare events include suicidal ideation and behavior.	Disulfiram-alcohol reaction, hepatotoxicity, optic neuritis, peripheral neuropathy, psychotic reactions.	Metabolic acidosis, acute myopia and secondary narrow-angle glaucoma, oligohydrosis and hyperthermia

Common side effects	Nausea, vomiting, decreased appetite, headache, dizziness, fatigue, anxiety.	Same as oral naltrexone, plus a reaction at the injection site; joint pain; muscle aches or cramps.	Diarrhea, somnolence.	Metallic after-taste, dermatitis, transient mild drowsiness.	Paresthesias, taste perversion, anorexia and weight loss, somnolence, cognitive dysfunction.
Examples of drug interactions	Opioid medications (blocks action).	Same as oral naltrexone.	No clinically relevant interactions known.	Anticoagulants such as warfarin; isoniazid; metronidazole; phenytoin; any nonprescription drug containing alcohol.	Other anticonvulsants, other carbonic anhydrase inhibitors, hydrochlorthiazide, metformin, pioglitazone, lithium, amitriptylene
Usual adult dosage	*Oral dose:* 50 mg daily. *Before prescribing:* Patients must be opioid-free for a minimum of 7 to 10 days before starting. If you feel that there's a risk of precipitating an opioid withdrawal reaction, administer a naloxone challenge test. Evaluate liver function. *Laboratory Followup:* Monitor liver function.	*IM dose*: 380 mg given as a deep intramuscular gluteal injection, once monthly. *Before prescribing:* Same as oral naltrexone, plus examine the injection site for adequate muscle mass and skin condition. *Laboratory Followup:* Monitor liver function.	*Oral dose*: 666 mg (two 333-mg tablets) three times daily; or for patients with moderate renal impairment (CrCl 30 to 50 mL/min), reduce to 333 mg (one tablet) three times daily. *Before prescribing:* Evaluate renal function. Establish abstinence.	*Oral dose:* 250 mg daily (range 125 mg to 500 mg). *Before prescribing:* Evaluate liver function. Warn the patient (1) not to take disulfiram for at least 12 hours after drinking and that a disulfiram-alcohol reaction can occur up to 2 weeks after the last dose and (2) to avoid alcohol in the diet (e.g., sauces and vinegars), over-the-counter medications (e.g., cough syrups), and toiletries (e.g., cologne, mouthwash). *Laboratory Followup:* Monitor liver function.	*Oral dose:* Initial dose 25 mg at bedtime, increasing the dose by 25-50 mg daily each week, divided into morning and evening doses. Faster titration is more likely to cause adverse reactions. Target dose is 200 mg per day total dose, but patients unable to tolerate that dose may respond to lower doses *Before prescribing:* Evaluate renal function, obtain serum electrolytes and bicarbonate *Laboratory Followup:* Monitor renal function, serum electrolytes and bicarbonate.

Note: This chart highlights some of the properties of each medication. It does not provide complete information and is not meant to be a substitute for the package inserts or other drug reference sources used by clinicians. For patient information about these and other drugs, the National Library of Medicine provides MedlinePlus (http://medlineplus.gov). Whether or not a medication should be prescribed and in what amount is a matter between individuals and their health care providers. The prescribing information provided here is not a substitute for a provider's judgment in an individual circumstance, and the NIH accepts no liability or responsibility for use of the information with regard to particular patients. Also note that while topiramate may be prescribed "off-label" by a physician, it has not yet been approved for the treatment of alcohol dependence by the FDA.

The information in this chart was drawn primarily from package inserts and references 1, 2, 4, 6, 8, and 12 .