

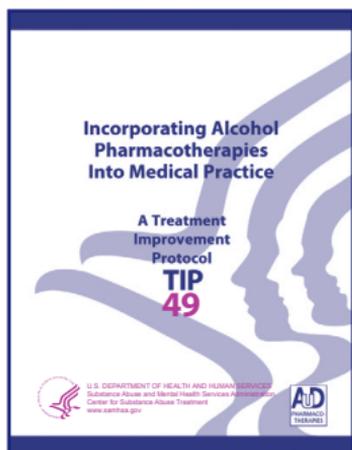
Quick Guide

For Physicians

Based on TIP 49

Incorporating Alcohol Pharmacotherapies Into

Medical Practice



U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Substance Abuse and Mental Health Services Administration
Center for Substance Abuse Treatment
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Incorporating Alcohol Pharmacotherapies Into Medical Practice

This Quick Guide is based entirely on information contained in TIP 49, published in 2009. No additional research has been conducted to update this topic since publication of TIP 49.

WHY A QUICK GUIDE?

This Quick Guide provides succinct, easily accessible information to physicians about the use of medications to help patients achieve and maintain abstinence from alcohol. It is based entirely on *Incorporating Alcohol Pharmacotherapies Into Medical Practice*, number 49 in the Treatment Improvement Protocol (TIP) series.

Users of this Quick Guide are invited to consult the primary source, TIP 49, for more information and a complete list of resources for alcohol use disorder (AUD) pharmacotherapies. To order a copy of TIP 49 or access it online, see the inside back cover of this Guide.

DISCLAIMER

The opinions expressed herein are the views of the consensus panel members and do not necessarily reflect the official position of the Center for Substance Abuse Treatment (CSAT), the Substance Abuse and Mental Health Services Administration (SAMHSA), or the U.S. Department of Health and Human Services (HHS). No official support of or endorsement by CSAT, SAMHSA, or HHS for these opinions or for the instruments or resources described are intended or should be inferred. The guidelines presented should not be considered substitutes for individualized patient care and treatment decisions.

WHAT IS A TIP?

The TIP series provides professionals in the substance abuse treatment and related fields with consensus-based, field-reviewed guidelines on substance abuse treatment topics of vital current interest. TIPs are published by CSAT, SAMHSA. The TIP series has been in production since 1991.

TIP 49, *Incorporating Alcohol Pharmacotherapies Into Medical Practice*, presents clinical guidelines on the proper use of four Food and Drug Administration (FDA)-approved medications for treating AUDs:

- Acamprosate (Campral)
- Disulfiram (Antabuse)
- Oral naltrexone (ReVia)
- Extended-release injectable naltrexone (Vivitrol).

INTRODUCTION

The intended audience for TIP 49 and this Quick Guide is physicians and other healthcare practitioners who can prescribe or administer medications for the treatment of AUDs, in either specialty substance abuse treatment programs or other healthcare settings, including physicians' offices.

Alcohol Dependence as a Chronic Illness

There is a strong similarity between substance dependence and other chronic illnesses (e.g., asthma, diabetes, hypertension) for which primary care physicians routinely provide pharmacotherapy and medical management. Genetics, personal choice, and environmental factors contribute to both substance dependence and other chronic conditions. Research into the pathophysiologic effects of alcohol and drugs—including enduring and possibly permanent neurophysiologic changes—provides further evidence that substance dependence is a chronic illness.

Medication-assisted treatment (MAT) of AUDs is consistent with treatment of other chronic illnesses such as diabetes or hypertension. Medication for AUDs may be used indefinitely or intermittently along with interventions aimed at changing lifestyle practices to sustain recovery.

Treating AUDs in Medical Settings

The high rates of AUDs in the United States make it likely that the healthcare practitioner is seeing patients with AUDs.

Most specialty substance abuse care is provided outside medical settings by nonmedical personnel (i.e., counselors) and is based on psychosocial approaches, such as cognitive-behavioral therapy and motivational enhancement, reinforced by participation in community-based mutual-help groups. However, many health problems and mental disorders that healthcare practitioners encounter derive from or are complicated by AUDs. Healthcare practitioners are in key positions to manage the care of patients with these disorders.

Screening, diagnosis, and treatment of AUDs in a physician's office offer advantages for patients with AUDs:

- Treatment is not delayed as can happen when practitioners refer patients to specialty AUD treatment.
- AUD treatment can be integrated with treatment for other medical disorders.
- Most patients are already familiar with the primary care setting and medical management of chronic conditions, which may reduce the stigma surrounding AUDs and their treatment.
- An ongoing relationship between a patient and healthcare practitioner may make referral to specialty substance abuse care more acceptable to a patient.

Management of the patient with an AUD may be seen in steps:

- Assessing the patient's suitability for treatment with a medication
- Determining which medication should be used

- Providing psychosocial services or referring the patient for these services concurrent with medication use
- Assessing the patient's response to medication, including both efficacy and side effects.

AUD treatment ranges from screening and brief intervention to specialty treatment, with different levels of care in between. Primary care practitioners can provide screening, brief interventions, and medical management.

Decisions about level of care, setting, and type of treatment are based on:

- Patient assessment
- Patient's commitment to change
- Treatment availability.

The most appropriate patients for brief interventions in a physician's office—and the least appropriate for long-term treatment in a substance abuse treatment program—are those whose drinking exceeds what is recommended, but who are not dependent.

Benefits of AUD Medications

MAT combined with brief intervention or more intensive levels of nonpharmacologic treatment can:

- Reduce protracted (postacute) withdrawal symptoms that can lead to a return to drinking
- Lessen cravings and urges to drink or use drugs
- Decrease impulsive or situational use of alcohol
- Lengthen periods of abstinence
- Prevent a lapse from becoming a full-blown relapse.

To date, FDA has approved four medications to treat AUDs:

- Acamprosate (Campral)
- Disulfiram (Antabuse)
- Oral naltrexone (ReVia)
- Extended-release injectable naltrexone (Vivitrol).

None of these medications “cures” AUDs the way an antibiotic cures bacterial pneumonia, and few Americans receive these AUD medications. However, as a part of comprehensive treatment, these medications may increase the likelihood of sustained remission from problem alcohol use. These medications make treatment in general medical settings a viable adjunct or alternative to specialty care.

For more detailed information, see TIP 49, Chapter 1—Introduction, pages 1–7.

ACAMPROSATE

Chemical name: Calcium acetyl homotaurinate.

Trade name: Campral.

How taken: Two delayed-release tablets by mouth three times per day, with or without food (a lower dose may be effective with some patients and *must* be used with those with impaired renal function).

How supplied: Enteric-coated 333 mg tablets.

Mechanism of Action

Acamprosate's mechanism of action has not been clearly established, but it is thought that it:

- Restores to normal the altered balance of neuronal excitation and inhibition from chronic alcohol use, possibly through interaction with the glutamate neurotransmitter system
- Helps modulate and normalize alcohol-related changes in brain activity
- Reduces symptoms of postacute (protracted) withdrawal, such as disturbances in sleep and mood that may trigger a relapse to drinking.

Appropriate Patients

Acamprosate may be most effective for patients who are motivated to achieve complete abstinence rather than decrease drinking. Because it does not interfere with opioids, this medication may be appropriate for patients who are:

- Receiving opioid maintenance therapy

- At risk of relapsing to opioid use
- Taking opioids for chronic or acute pain.

Safety

Acamprosate has a good safety profile:

- Patients will not develop tolerance to or dependence on acamprosate.
- Acamprosate appears to have no potential for abuse.
- It has virtually no overdose risk.
- Most side effects are mild and temporary.
- Acamprosate can be continued safely if a patient relapses to drinking and then requires detoxification.
- It is safe for patients who are taking many medications for multiple medical issues because there are no clinically significant drug interactions.
- It is not metabolized by the liver and can be used safely by patients with severe liver disease.
- It can be used with patients receiving opioid maintenance therapy or opioids for acute or chronic pain.

Initiating Treatment

Before initiating treatment:

- Conduct a thorough medical exam and assessment
- Perform renal function tests (a standard panel for urea, electrolytes, and serum creatinine) to rule out severe renal impairment.

Acamprosate is typically started 5 days after the patient stops drinking, although it can be started during medically supervised withdrawal. It can be used

safely with benzodiazepines. Acamprosate should be continued if a patient relapses to alcohol use. Acamprosate reaches full effectiveness in 5 to 8 days.

Contraindications

Do not prescribe acamprosate for patients with:

- Previous hypersensitivity to acamprosate or its components
- Severe renal impairment (creatinine clearance ≤ 30 mL/minute).

Prescribing Cautions

Use caution when prescribing for:

- **Patients with moderate renal impairment.** For creatinine clearance of 30–50 mL/minute, reduce dosage to one 333 mg tablet three times per day.
- **Adults ages 65 and older.** Because of a higher risk of diminished renal function in this age group, perform frequent renal function tests; acamprosate has not been evaluated for safety or efficacy in this group.
- **Women who are pregnant or nursing.** Avoid using unless potential benefits outweigh risks.
- **Children and adolescents.** Safety and efficacy have not been determined.

Side Effects

- **Most common.** Diarrhea and drowsiness.
- **Least common.** Intestinal cramps, flatulence, nausea, headache, increased or decreased libido, insomnia, anxiety, muscle weakness, itchiness, and dizziness.

Patients should be instructed not to discontinue acamprosate if they experience side effects but to inform their prescriber.

Adverse Reactions	Management
Suicidal ideation, suicide attempts (very uncommon, but serious)*	<p>Inform patients to contact the prescribing professional immediately</p> <p>Monitor patients for onset or worsening of depression</p> <p>Obtain a psychiatric consult or prescribe antidepressant medication, as necessary</p> <p>Discontinue acamprosate</p>
Severe or persistent diarrhea	<p>Treat with Imodium or Pepto-Bismol</p> <p>Recommend appropriate dietary changes</p> <p>Reduce acamprosate dosage or discontinue use if diarrhea remains intolerable after treatment</p>

*Suicidal ideation is closely linked with substance use disorders, with or without acamprosate use. More information about managing the risk can be found at the National Suicide Prevention Resource Center's Web site (<http://www.sprc.org>) and at the Suicide Prevention for Physicians Web page (<http://suicideandmentalhealthassociationinternational.org/preventionphy.html>).

Patient Education

Patients should understand that:

- They should notify the prescriber immediately if they have suicidal thoughts or feel depressed or if an existing depression worsens.
- Acamprosate reaches full effectiveness in 5–8 days.
- Patients should continue taking acamprosate if they slip or relapse, and they should inform their prescriber immediately.
- Tablets should not be crushed.
- Patients should not take extra medication if they miss a dose.

Treatment Duration and Discontinuing Acamprosate

Discontinuation of acamprosate may be considered when a patient:

- Has achieved stable abstinence, reports diminished craving, and has established a sound plan and support for ongoing recovery
- Is not adhering to the medication regimen.

Acamprosate should not be discontinued if a patient returns to alcohol use. Stopping acamprosate will not precipitate withdrawal syndrome; it is not necessary to taper the dose.

For more detailed information, see TIP 49, Chapter 2—Acamprosate, pages 9–14.

DISULFIRAM

Chemical name: Bis(diethylthiocarbamoyl) disulfide.

Trade name: Antabuse.

How taken: Tablet by mouth once daily (also may be crushed and mixed with water, coffee, tea, milk, soft drink, or fruit juice).

How supplied: 250 or 500 mg tablets.

Mechanism of Action

Disulfiram inhibits aldehyde dehydrogenase, causing a reaction of flushing, sweating, nausea, and tachycardia when alcohol is ingested.

Disulfiram–Alcohol Aversive Reaction

Disulfiram is an alcohol-aversive agent. It causes an acutely toxic physical reaction when mixed with alcohol. Disulfiram may not reduce the urge to drink alcohol, but patients' expectation of the possible severe reaction if they drink alcohol may increase their motivation to remain abstinent.

The aversive effects:

- Vary from patient to patient
- Typically begin about 10 to 30 minutes after alcohol is ingested
- Are generally proportional to the amounts of disulfiram and alcohol ingested
- May occur for up to 14 days after the last ingested dose of disulfiram
- Can range from moderate to severe.

Moderate aversive effects:

- Sweating
- Warmth and flushing, particularly on upper chest and face
- Hyperventilation, respiratory difficulty/dyspnea
- Acetaldehyde breath odor, blurred vision, head and neck throbbing, thirst
- Nausea/vomiting
- Chest pain/palpitations, hypotension, tachycardia
- Vertigo, syncope, marked uneasiness, confusion
- Weakness.

Severe aversive effects:

- Respiratory depression
- Arrhythmias, cardiovascular collapse
- Myocardial infarction (in individuals with preexisting coronary artery disease)
- Acute congestive heart failure (in individuals with preexisting myocardial dysfunction)
- Seizures, unconsciousness
- Death.

Managing a Severe Disulfiram–Alcohol Reaction

When effects are severe, supportive measures may be needed to restore blood pressure and treat shock. Administration of oxygen or carbogen (95 percent oxygen, 5 percent carbon dioxide), intravenous (IV) vitamin C (1 g), ephedrine sulfate, or IV antihistamines may be indicated. Check potassium levels in patients on digitalis because hypokalemia has been reported.

Appropriate Patients

- Patients motivated for treatment and committed to total abstinence
- Patients capable of understanding the consequences of drinking alcohol while taking disulfiram
- Patients who have undergone detoxification or are in the beginning stage of abstinence and can receive adequate, ongoing supervision
- Patients who also abuse cocaine.

Safety

Deaths from the disulfiram–alcohol aversive reaction are now rare because of lower dosages, and patients with severe cardiac disease are excluded from disulfiram treatment.

Disulfiram Black-Box Warning

Disulfiram should never be administered to a patient who is in a state of alcohol intoxication or without the patient's full knowledge. The physician should instruct relatives accordingly.

Initiating Treatment

Before initiating treatment:

- Conduct a physical exam
- Obtain a medical and psychiatric history, including allergies to disulfiram
- Give a breath or blood alcohol test if such a test is clinically indicated to confirm the patient has abstained from alcohol for at least 12 hours and/or the breath or blood alcohol level is zero

- Test liver function: alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyltransferase (GGT), alkaline phosphatase, lactate dehydrogenase, bilirubin, total protein, albumin, prothrombin time
- Test kidney function: routine blood urea nitrogen (BUN), creatinine
- Obtain a complete blood count, routine chemistries, if clinically indicated
- Get an electrocardiogram for those with a history of heart disease
- Test for pregnancy in women of childbearing age
- Educate the patient about disulfiram
- Obtain informed consent.

Prescribing Cautions

Use caution when prescribing for:

- **Patients with severe myocardial disease or coronary occlusion.** Avoid using disulfiram unless potential benefits outweigh risks of ongoing alcohol abuse.
- **Patients with histories of cardiac disease, diabetes mellitus, hypothyroidism, epilepsy, cerebral damage, and chronic or acute nephritis.**
- **Patients with hepatitis C.** Use with careful monitoring of liver function if baseline transaminase levels are normal or only moderately elevated (< 5 times the upper limit of normal).
- **Adults ages 61 and older.** May need to decrease dosage.

- **Women who are pregnant or nursing.** Avoid using unless potential benefits outweigh risks; patients should stop nursing before taking disulfiram.
- **Children and adolescents.** Safety and efficacy have not been determined.
- **Patients with psychosis.** Use with caution in treated, stable patients only.

Dosages

- **Initial dosage.** 250 mg/day in 1 morning or evening dose for 1–2 weeks.
- **Average maintenance dosage.** 250 mg/day.
- **Dosage range.** 125–500 mg/day.
- **Maximum dosage.** 500 mg/day.

The following substances must be out of the patient's system before he or she takes disulfiram:

- Metronidazole
- Paraldehyde
- Alcohol or alcohol-containing preparations (e.g., cough syrups, tonics)
- Ethylene dibromide or its vapors (e.g., in paint, paint thinner, varnish, shellac).

Patients on a seemingly adequate disulfiram dosage who report that they can drink with impunity could be disposing of their tablets without taking them. Prescribers should not conclude that disulfiram is ineffective until patients are proved to have been taking their daily tablets. Once adherence is confirmed in the patient who reports ability to drink alcohol, the physician

should consider increasing the disulfiram dosage (never exceed 500 mg/day) or prescribing a different medication.

Followup Testing

- Repeat liver function tests (i.e., ALT, AST, GGT, bilirubin) 10–14 days after initiation of therapy, then monthly for 6 months, then every 3 months for duration of treatment
- Perform a pregnancy test monthly for women of childbearing age
- Test for BUN and creatinine, as clinically indicated
- Use urine toxicology screen when concern exists about unreported alcohol or drug use.

Side Effects

The following side effects can occur during the first 2 weeks and wane either spontaneously or after a decrease in the disulfiram dosage:

- Skin/acneiform eruptions
- Allergic dermatitis (often can be managed with concomitant antihistamines)
- Mild drowsiness
- Fatigue
- Headache
- Impotence
- Metallic aftertaste.

Instruct patients who feel sedated from disulfiram to take it at bedtime. If daytime sedation persists, decrease the dosage.

Uncommon Adverse Reactions	Management
Optic neuritis	Discontinue disulfiram, and conduct an ophthalmologic examination
Peripheral neuritis, polyneuritis, peripheral neuropathy	Discontinue disulfiram, and observe patient or refer patient for neurological evaluation
Hepatitis (cholestatic and fulminant hepatitis, hepatic failure)	Discontinue disulfiram immediately when clinical or laboratory evidence of hepatic dysfunction is found Perform a medical history and physical examination, and obtain liver function test Maintain clinical monitoring of symptoms and liver function, and follow findings to resolution
Psychosis	Reduce or discontinue disulfiram, and treat underlying psychosis as indicated

Patient Education

Patients should understand:

- The disulfiram–alcohol aversive reaction
- Benefits and limitations of disulfiram
- The need to avoid products that contain disguised alcohol (e.g., vinegars, sauces, aftershave lotions, liniments)
- When scheduled for surgery, the importance of telling physicians or dentists that they are taking disulfiram
- The importance of carrying a safety identification card indicating that the patient is taking disulfiram, symptoms of possible disulfiram–alcohol aversive reactions, and the physician or institution to contact in an emergency
- The need to report symptoms of potential neurologic or liver injury immediately to the physician.

Treatment Duration and Discontinuing Disulfiram

- Daily dosing may continue for months or years until the patient has established stable, long-term alcohol abstinence.
- Patients must be warned that disulfiram–alcohol reactions may occur as long as 2 weeks after stopping the medication.

For more detailed information, see TIP 49, Chapter 3—Disulfiram, pages 15–26.

ORAL NALTREXONE

Chemical name: Naltrexone hydrochloride.

Trade name: ReVia.

How taken: Tablet by mouth once daily.

How supplied: 50 mg tablets. Generic version also available.

Mechanism of Action

The mechanism of action is not clearly understood. Naltrexone is a long-lasting opioid antagonist used to treat opioid dependence and AUDs. Naltrexone reduces both the rewarding effects of alcohol and craving for it. By blocking craving, naltrexone may help patients abstain from drinking. By blocking the pleasure from alcohol, naltrexone may reduce the amount of heavy drinking in those who do drink.

Appropriate Patients

- Patients with intense alcohol cravings may experience greater benefit than patients with low levels of alcohol craving.
- When treated with naltrexone, patients with more somatic complaints may have better outcomes than do patients with less physical distress.
- Patients with a family history of alcohol dependence may benefit more from naltrexone treatment than patients without a family history of alcohol dependence.

- Naltrexone's opioid antagonist properties make it a good treatment option for individuals who have both an AUD and a history of opioid abuse/dependence and are currently abstinent from opioids.

Safety

Naltrexone has virtually no abuse potential, and patients do not develop tolerance.

Naltrexone is an opioid antagonist, so individuals receiving naltrexone who are opioid dependent may experience opioid withdrawal. Patients must be opioid free for 7 to 10 days (or at least 14 days for patients who have been taking methadone for more than 3 to 4 weeks), as determined by medical history or toxicological screening.

Naltrexone has few adverse effects. However, naltrexone's FDA-approved label includes a warning regarding hepatotoxicity. These reversible effects tend to be associated with much higher doses (e.g., 300 mg/day or more) than those used in routine clinical practice and tend to occur after a patient is on such high doses for extended periods.

Initiating Treatment

Before initiating treatment:

- Perform liver function tests (i.e., ALT, AST, GGT, bilirubin) to establish suitability for medication and a baseline
- Discuss the risks of naltrexone use during pregnancy and advise women of childbearing age to use birth control while taking naltrexone

Oral Naltrexone Black-Box Warning

Naltrexone has the capacity to cause hepatocellular injury when given in excessive doses.

Naltrexone is contraindicated in acute hepatitis or liver failure, and its use in patients with active liver disease must be carefully considered in light of its hepatotoxic effects.

The margin of separation between the apparently safe dose of naltrexone and the dose causing hepatic injury appears to be only fivefold or less. Naltrexone does not appear to be a hepatotoxin at the recommended doses.

Patients should be warned of the risk of hepatic injury and advised to stop the use of naltrexone and seek medical attention if they experience symptoms of acute hepatitis.

- Obtain a drug use history and perform toxicological screening to ensure that patients are not regular users of opioids (illicit drugs, opioid maintenance medications [e.g., methadone, buprenorphine, buprenorphine with naloxone], or opioid pain medications)
- Strongly caution patients of the unpleasant physical effects of opioid withdrawal that will result if patients are not completely detoxified from opioids before taking their first dose of naltrexone.

Practitioners should not begin treatment until a patient's acute alcohol withdrawal has subsided. At least 3 days of abstinence are usually recommended, with as many as 7 days if possible. Patients may experience fewer medication side effects (particularly nausea) if they are abstinent from alcohol when they start naltrexone. If it is clinically indicated, patients may begin taking naltrexone during medically supervised withdrawal or if they are actively drinking.

Contraindications

Do not prescribe oral naltrexone if the patient:

- Is currently using opioids (as indicated by self-report or a positive urine drug screen)
- Is on buprenorphine (Suboxone or Subutex) or methadone maintenance therapy for opioid dependence
- Is currently undergoing opioid withdrawal
- Has acute hepatitis or liver failure
- Will need opioid analgesics within 7 days
- Is sensitive to naltrexone, structurally similar compounds (e.g., naloxone or nalmefene), or an inactive ingredient in the tablet.

Prescribing Cautions

Use caution when prescribing for:

- **Patients with active liver disease.** Monitor liver function carefully.
- **Patients with moderate to severe renal impairment.** Monitor renal function carefully.
- **Pregnant and nursing women.** Do not prescribe unless potential benefits outweigh risks.

- **Women of childbearing age.** Encourage use of effective birth control method.
- **Patients whose serum aminotransferase results are > 5 times the upper limit of normal.** Generally avoid prescribing unless potential benefits outweigh risks.
- **Patients who have chronic pain syndromes with acute or recurring need for opioid analgesics.** Ensure patients abstain from naltrexone for 3–7 days before beginning opioid analgesics.

Dosages

- **Initial dosage for most patients.** 50 mg/day in a single tablet.
- **Initial dosage for patients at risk of adverse events** (e.g., young patients, those with shorter abstinence). 12.5 mg/day (it is okay to break tablets) or 25 mg/day for 1 week (2 weeks, if necessary), with food; gradually increase to 50 mg/day.
- **Average maintenance dosage.** 50 mg/day.

Side Effects

Side effects are generally mild and often diminish over time. Less common reactions and some potentially serious reactions have been reported.

Common side effects:

- Nausea/vomiting
- Headache
- Dizziness
- Fatigue/somnolence
- Nervousness
- Anxiety.

Less common side effects:

- Diarrhea, constipation, stomach pains, cramps, excessive thirst, loss of appetite
- Chest pain
- Joint/muscle pain
- Rash
- Difficulty sleeping
- Sweating
- Increased tears, mild depression
- Delayed ejaculation.

Adverse Reactions	Management
Nausea	Suggest the patient not take naltrexone on an empty stomach; take it with complex carbohydrates or a tablespoon of simethicone or bismuth subsalicylate Reduce dose or stop for 3–4 days, then restart at a lower dose
Liver toxicity	Discontinue naltrexone
Precipitated opioid withdrawal	Discontinue naltrexone; provide supportive treatments (i.e., hydration, antispasmodic, and antidiarrheal medications); give an α -2-agonist (e.g., clonidine) to relieve symptoms
Naltrexone overdose	Treat symptomatically and monitor closely; contact poison control for most recent information

Pain Management for Patients on Naltrexone

As an opioid antagonist, naltrexone blocks the effects of opioid analgesics. Typical doses of opioid analgesics (e.g., codeine, morphine, oxycodone, hydrocodone) may not be effective to relieve pain.

When opioids must be used, it is possible to reverse the naltrexone blockade using higher than usual doses of opioids. However, because of the potential for opioid-induced respiratory depression, this should be done only in medical settings with the provision for respiratory support. A rapidly acting opioid analgesic is recommended to minimize the duration of respiratory depression. Again, patients should be monitored closely.

Naltrexone does not block aspirin, acetaminophen, or nonsteroidal anti-inflammatory drugs; local anesthetics; or general (nonopioid) anesthetics.

Patient Education

Patients should understand that:

- The symptoms of protracted alcohol withdrawal (e.g., sleep disturbance) may overlap with side effects of naltrexone.
- These symptoms typically improve with time.
- Taking large amounts of opioids to overcome naltrexone's blockade of the opiate receptors increases the risk of overdose, respiratory arrest, coma, and death.

- Patients may be more sensitive to lower doses of opioids after taking naltrexone for some time and then stopping it than they were before naltrexone treatment. This means they risk overdose if they take opioids in the same amount as they took before naltrexone treatment.
- Patients should continue to take naltrexone if they relapse to alcohol use; it may help limit the severity of relapse.
- Patients should carry a medical alert card that indicates they are taking naltrexone and lists the prescribing physician or institution to contact in an emergency.
- Patients should not take opioid medications for at least 3 days after stopping naltrexone.

Treatment Duration and Discontinuing Oral Naltrexone

- The optimal length of treatment has not been established.
- Tailor the length of treatment to individual patients.
- It is not necessary to taper the dose.

For more detailed information, see TIP 49, Chapter 4—Oral Naltrexone, pages 27–35.

EXTENDED-RELEASE INJECTABLE NALTREXONE

Chemical name: Naltrexone for extended-release injectable suspension.

Trade name: Vivitrol.

How taken: Intramuscular (IM) injection once every 4 weeks.

How supplied: Single-use carton containing 380 mg vial of Vivitrol microspheres, 4 mL vial of diluent, 5 mL syringe, 20-gauge ½-inch needle, and two 20-gauge 1½-inch needles.

Storage: Refrigerate (2–8 °C, 36–46 °F); store unrefrigerated at temperatures not exceeding 25 °C (77 °F) for no more than 7 days; do not freeze.

Availability: Injectable naltrexone is available through specialty pharmacies.

Mechanism of Action

Extended-release injectable naltrexone is a microsphere formulation of the opioid antagonist medication naltrexone. The extended-release injectable form helps address patient nonadherence. The mechanism of action is the same as that for oral naltrexone.

Plasma concentration peaks approximately 2 hours after an IM injection of naltrexone followed by a second peak 2–3 days later. Seven days after dosing, plasma concentrations slowly decline, maintaining a therapeutic naltrexone blood level over 4 weeks. Unlike oral

naltrexone, injectable naltrexone does not undergo first-pass metabolism in the liver.

Appropriate Patients

Injectable naltrexone may be beneficial to patients who have not responded to other pharmacological and behavioral treatments for AUD, particularly those who have problems with medication adherence. It could be considered a first-line therapy for any patient who is alcohol dependent, interested in treatment, and not subject to the contraindications.

For optimal results with injectable naltrexone, candidates for treatment should be:

- Abstinent for at least 4 days
- Motivated to maintain abstinence or to reduce their drinking
- Willing to participate in psychosocial substance abuse treatment such as counseling and support groups.

Candidates should:

- **Not** be using opioids currently or recently
- **Not** be anticipating surgery or have a condition, such as chronic pain, for which opioid analgesics may be needed in the future.

Safety

Injectable naltrexone appears to be well tolerated, with side effects similar to those of oral naltrexone (with the exception of injection-site reactions). It carries a black-box warning regarding liver toxicity (see page 23).

However, because of its lack of first-pass metabolism, injectable naltrexone significantly reduces liver exposure to the drug, reducing the risk of potential liver toxicity.

Naltrexone is an opioid antagonist, so individuals who are opioid dependent and receiving IM naltrexone may experience opioid withdrawal. Patients must be opioid free for 7 to 10 days (or at least 14 days for patients who have been taking methadone for more than 3 to 4 weeks), as determined by medical history or toxicological screening.

Initiating Treatment

Before initiating treatment:

- Conduct a physical examination
- Perform liver function tests (i.e., ALT, AST, GGT, bilirubin)
- Obtain toxicological screening test results.

Patients taking buprenorphine or methadone for the treatment of opioid dependence cannot receive IM naltrexone.

Before injecting naltrexone, physicians should advise patients of the unpleasant physical effects of opioid withdrawal that will result if patients are not completely detoxified from opioids before their first injection of naltrexone.

Prescribing Cautions

Use caution when prescribing for:

- **Patients with thrombocytopenia or coagulation disorders.** Monitor carefully for 24 hours after injection.

- **Patients with recent opioid dependence.** Explain risks of precipitated withdrawal, the opioid-blocking effects, and the significant risk of return to opioid use.
- **Patients whose body mass precludes IM injection with the provided 1½-inch needle.** Be aware that inadvertent subcutaneous injection may cause a severe injection-site reaction.

Administering Injectable Naltrexone

Injectable naltrexone should be administered only by a medical professional who can dispense IM injections. Proper IM injection technique is essential. Serious injection-site reactions, sometimes requiring extensive surgical debridement, have occurred and may be more common if the product is inadvertently administered subcutaneously instead of intramuscularly. Some pain and tenderness similar to any IM injection or a small lump frequently develops at the injection site but resolves in 2–4 weeks.

Side Effects

- Injection-site reactions (sometimes severe)
- Nausea/vomiting
- Headache
- Dizziness
- Fatigue
- Back pain
- Upper abdominal pain
- Decreased appetite.

Adverse Reactions and Their Management

Possible adverse reactions are the same as those for oral naltrexone (see page 26) plus possible severe injection-site reactions. Patients should be instructed to seek immediate medical attention if the injection site becomes painful, red, and swollen and does not improve within 1 week after the injection. Patients receiving injectable naltrexone also should be monitored for depression and for symptoms of liver disease.

Patient Education

Patients should understand that:

- Naltrexone's onset occurs within several hours, although full effectiveness may not develop for 2 to 3 days after the first injection.
- Once naltrexone is injected, it is impossible to remove it from the body; the effects can last up to 4 weeks.
- Other options for analgesia exist besides opioid medication.
- Injectable naltrexone blocks low to moderate doses of opioids, but large doses of heroin or other opioids may lead to overdose and serious injury, coma, or death.
- Injectable naltrexone may lower tolerance for opioids in patients with a history of opioid use, resulting in a greater sensitivity to lower doses of opioids after injectable naltrexone treatment is stopped. If regular amounts of opioids are taken, respiratory depression and overdose may occur.

Pain Management

Pain management for patients receiving injectable naltrexone can be more complicated than with oral naltrexone because the medication is long acting. The package insert states:

In an emergency situation in patients receiving Vivitrol, a suggested plan for pain management is regional analgesia, conscious sedation with a benzodiazepine, and use of non-opioid analgesics or general anesthesia.

In a situation requiring opioid analgesia, the amount of opioid required may be greater than usual, and the resulting respiratory depression may be deeper and more prolonged.

A rapidly acting opioid analgesic which minimizes the duration of respiratory depression is preferred. The amount of analgesic administered should be titrated to the needs of the patient. Non-receptor mediated actions may occur and should be expected (e.g., facial swelling, itching, generalized erythema, or bronchoconstriction), presumably due to histamine release.

Irrespective of the drug chosen to reverse Vivitrol blockade, the patient should be monitored closely by appropriately trained personnel in a setting equipped and staffed for cardiopulmonary resuscitation.

- The opioid-blocking effects last for at least 4 weeks and the risks associated with a return to opioid use are significant.
- Patients should carry a safety ID card that indicates they are taking injectable naltrexone.

Treatment Duration and Discontinuing Injectable Naltrexone

The optimal length of treatment has not yet been defined. Healthcare practitioners may consider discontinuing injectable naltrexone once a patient has achieved stable abstinence from alcohol and has established a sound plan for ongoing recovery or if a patient does not adhere to the medication regimen.

For more detailed information, see TIP 49, Chapter 5—Extended-Release Injectable Naltrexone, pages 37–44.

PATIENT MANAGEMENT

Persons with AUDs often have physical and social sequelae. Alcohol dependence can harm many organ systems, and certain conditions may preclude pharmacotherapy with any of these medications.

Initial Assessment

Thorough assessments for substance use and social, medical, and psychiatric histories are needed to evaluate consequences of dependence and identify problems that can be addressed with treatment. Evaluation can identify or rule out contraindications to pharmacotherapy.

Physical exam

Patients with AUDs may have no specific abnormal exam findings. However, when present, abnormal exam findings provide evidence of the severity of a patient's AUD. Longstanding alcohol consumption may present with many physical features, including:

- Physical manifestations of cirrhosis
- Encephalopathy
- Vitamin deficiencies.

Alcohol consumption can incur:

- Tachycardia
- Tremors
- Elevated blood pressure
- Hepatosplenomegaly
- A tender liver edge
- Peripheral neuropathy

- Spider angiomata
- Conjunctival injection
- Unexplained signs of trauma.

Laboratory testing

No single laboratory test is sensitive or specific for AUD diagnoses. Detection of AUDs is improved when laboratory tests are combined with other screening strategies (e.g., questionnaires). The following tests can help healthcare practitioners identify AUDs and possible alcohol-related abnormalities:

- Blood/breath/urine alcohol and toxicological screenings measure recent alcohol consumption.
- Serum carbohydrate-deficient transferrin (CDT) levels are not often used in primary care practice, but they may be used to screen for chronic alcohol consumption and to monitor consumption during treatment. For example, an increase in CDT over time may suggest an increase in alcohol consumption.
- AST and GGT are often elevated in persons who recently consumed significant amounts of alcohol. AST, GGT, and CDT may be most useful for screening when used in combination.
- Ethyl glucuronide (EtG) testing is increasingly being used for screening and is highly sensitive to alcohol use. However, exposure to even small amounts (such as those found in some foods and cosmetic items) can trigger a false positive test result.

The following tests can be used to identify alcohol-related damage and medication contraindications:

- **Complete blood count.** Alcohol overuse causes anemia and has toxic effects on bone marrow. Many persons who are alcohol dependent have macrocytosis and an elevated mean corpuscular volume.
- **Tests for vitamin deficiencies.** Thiamine, folic acid, and pyridoxine deficits are common in people with chronic AUDs.
- **Hepatic and renal tests.** Consideration of pharmacotherapy treatment of AUDs requires evaluating organ systems that metabolize and excrete these medications. Naltrexone and disulfiram should be used with caution in patients with liver disease. Naltrexone and acamprosate should be used with caution in patients with renal impairment. Therefore, hepatic and renal system testing should be done before initiating any of these medications.
- **Pregnancy test.** All four medications used to treat AUDs are FDA pregnancy category C; women of childbearing age should receive a pregnancy test before pharmacotherapy is initiated.

Providing feedback about patients' initial test results, compared with norms, and the health risks associated with these results can be a way to increase patients' motivation and adherence to treatment. Laboratory tests help healthcare practitioners objectively monitor patients' progress and provide patients with objective

reinforcement by demonstrating biologic evidence of their improving health status.

Psychiatric assessment

Psychiatric conditions frequently occur with excessive alcohol consumption. Some psychiatric symptoms resolve or lessen with abstinence. Untreated psychiatric conditions can seriously interfere with a patient's ability to adhere to pharmacotherapy and psychosocial treatment for alcohol dependence and can cause the patient preventable suffering.

The prescribing professional should assess the patient for:

- Psychiatric disorders
- Suicidal ideation or intent.

Substance use assessment

- Quantity, frequency, and pattern of alcohol use (e.g., persistent, occasional, binge use); episodes of use; duration of use; and consequences of alcohol consumption
- Use of substances other than alcohol, especially opioids, and use, misuse, or abuse of prescription medications
- Detoxification episodes
- Previous pharmacotherapy interventions
- Specialty substance abuse treatment episodes (including when, where, modality, duration, and outcome)
- Individual therapy
- Mutual- or self-help program involvement.

Social history

- Family situation including partners and anyone who should be included in treatment planning or could monitor a patient's medication adherence
- Living situation
- Employment status.

Assessing motivation for change

Ask patients:

- In what ways are you concerned about your drinking?
- How much does this concern you?
- What are your reasons for making a change?
- How do you feel about changing your drinking?
- How ready are you to change your drinking?
- What do you think will happen if you don't make a change?
- What do you think you want to do about your drinking?
- What do you think would work for you, if you needed to change?

Choosing a Medication

Consider:

- Experience with and adherence to maintenance medications
- Patient's opinion about which medication may be most helpful
- Level of motivation for abstinence
- Medical status and contraindications for each medication.

AUD Medication Decision Grid

Pretreatment Indicators	Acamprosate	Disulfiram	Oral Naltrexone	Injectable Naltrexone
Renal failure	X	A	C	C
Significant liver disease	A	C	C	C
Coronary artery disease	A	C	A	A
Chronic pain	A	A	C	C
Current opioid use	A	A	X	X
Psychosis	A	C	A	A
Unable to sustain total abstinence	A	X	A	A
History/risk factors for poor medication adherence	C	C	C	A
Diabetes	A	C	A	A
Obesity that precludes deep IM injection	A	A	A	X
Family history of AUDs	A	A	+	+
Bleeding or other coagulation disorder	A	A	A	C
High level of craving	A	A	+	+
Opioid dependence in remission	A	A	+	+
History of postacute withdrawal syndrome	+	A	A	A
Cognitive impairment	A	X	A	A

A = Appropriate to use
X = Contraindicated

C = Use with caution
+ = Particularly appropriate

Psychosocial Intervention

Any pharmacologic treatment for alcohol dependence should be used in conjunction with psychosocial treatment. Medication and psychosocial therapy combined are more effective than either alone.

Specialty substance abuse treatment addresses immediate withdrawal and craving and management of long-term abstinence through:

- Pharmacotherapy
- Case monitoring
- Individual, group, and family/couples counseling and therapy
- Other psychosocial services (e.g., vocational counseling)
- Referral to mutual-help groups.

Specialty substance abuse treatment programs provide a range of complementary services. A practitioner who treats patients with alcohol dependence should:

- Become familiar with local treatment resources and develop relationships with treatment staff that will facilitate referrals and followup
- Understand programs' treatment duration, modality, philosophy, and continuing-care options to help match a patient to appropriate treatment; prepare the patient for what to expect; and enhance adherence to the referral.

Practitioners can find programs in their areas by using the interactive SAMHSA Web site at <http://dasis3.samhsa.gov>.

Developing a Treatment Plan

A comprehensive pharmacotherapy treatment plan for a patient with an AUD should include the following:

- The medication to be used and a rationale for its use
- Initial and maintenance dosages
- A schedule for followup office visits and laboratory testing for monitoring health status and progress
- Criteria for discontinuing the medication
- A referral and followup plan for concurrent specialty substance abuse treatment, psychiatric treatment, and/or family therapy
- A plan for mutual- or self-help group attendance
- Clarification of family or significant other involvement in treatment
- A plan for treating alcohol-related or other concurrent conditions.

Monitoring Patient Progress

Treatment adherence

- Tracking patients' record of keeping appointments for medication monitoring
- Monitoring prescription refills
- Noting whether patients are keeping agreements about payment for treatment
- Requesting periodic status reports from specialty substance abuse treatment programs, psychiatric referrals, and other psychosocial therapy or support.

Abstinence or reduced alcohol consumption

- Patient self-reports of quantity and frequency of drinking, especially during stressful periods (e.g., holidays, celebrations, major life changes)
- Laboratory tests including AST, GGT, CDT, EtG, and urine drug screening
- Breathalyzer tests (although breathalyzer tests detect alcohol ingestion only for a short period).

The practitioner can use this information to provide positive feedback to patients who are successful in maintaining abstinence.

Craving

More important than the method of monitoring is consistency in how the patient is asked about craving patterns and trends. Ask patients about:

- Current craving
- Cravings over the past week (e.g., as a rating between 1 and 10, with 1 being no craving and 10 the most intense craving the patient has ever experienced)
- Any episodes that have caused particular problems for the patient
- Patterns of craving over time.

Health status and social functioning

It is important to monitor patients' progress over time in the following areas:

- Health
- Family/social activities
- Work/vocational status

- Legal status
- Mental status.

Other substances of abuse

- The abuse of other substances can be evaluated by random urinalysis collection and testing and self-reports from the patient.
- The use of illicit substances, tobacco use, and abuse of prescription and nonprescription medications should be addressed.
- The patient's agreement or resistance to continuing treatment may indicate his or her willingness to consider other substance use a problem.

Modifying the Treatment Plan

Modifications may need to be made when:

- A patient is not responding to one medication but may respond to another.
- A patient's goals change.
- A patient relapses.

If the patient relapses, the practitioner has several options:

- Increase monitoring of medication adherence
- Increase the medication dose
- Change the medication
- Increase or change the intensity of psychosocial treatment and/or refer the patient to specialty care
- Examine social, medical, or behavioral factors that contribute to alcohol consumption.

Patients who chronically relapse may need to be referred to addiction professionals in specialty treatment settings.

Mutual- or Self-Help Programs

Mutual- or self-help group support can be critical to long-term recovery. Practitioners should learn about local groups so they can provide that information to their patients and discuss patients' participation. Lists of local meetings can be obtained from the Web and given to patients.

Patient Education Topics

- Alcohol dependence as a chronic medical disorder
- What to expect in recovery, including symptoms of postacute withdrawal
- Possible benefits of a particular medication
- Medication information:
 - How and when to take it
 - Importance of adhering to the regimen
 - When the medication becomes effective
 - Possible common side effects and their expected duration
 - Under what conditions the patient should immediately call the practitioner, such as symptoms of liver problems or other serious adverse events
 - Any cautions regarding daily activities (e.g., not driving until the effects of a medication are known)

- Medication interactions
- Aids to medication adherence, such as blistercard packs, pill boxes, alarms, or asking a family member to remind patient
- Importance for women of childbearing age to use an effective birth control method
- What to do if relapse occurs
- Importance of concurrent psychosocial treatment and mutual- or self-help programs
- Followup plans.

Discontinuing Pharmacotherapy

The patient and practitioner may consider discontinuing medication under the following conditions:

- Patient reports substantially diminished craving.
- Patient has maintained stable abstinence over a sustained period.
- Patient feels ready to discontinue the medication.
- Patient is engaged in ongoing recovery, including community supports (such as attendance at mutual-help group meetings).

None of the medications discussed in this Quick Guide produce a withdrawal syndrome, and they do not need to be tapered.

For more detailed information, see TIP 49, Chapter 6—Patient Management, pages 45–61.

Ordering Information

TIP 49

Incorporating Alcohol Pharmacotherapies Into Medical Practice

TIP 49-Related Products

KAP Keys for Clinicians Based on TIP 49
(SMA) 10-4544

Quick Guide for Counselors Based on TIP 49
(SMA) 10-4542

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Three Ways to Obtain FREE Copies of All TIP Products

1. Call SAMHSA's Health Information Network (SHIN) at **1-877-SAMHSA-7 (1-877-726-4727)** (English and Español).
2. Visit SHIN's Web site at **<http://www.samhsa.gov/shin>**.
3. Access products online at **<http://www.kap.samhsa.gov>**.



Other HHS products that are relevant to this Quick Guide:

TIP 24: *A Guide to Substance Abuse Services for Primary Care Clinicians (SMA) 08-4075*

TIP 45: *Detoxification and Substance Abuse Treatment (SMA) 08-4131*

See the inside back cover for ordering information for all TIPs and related products.

The following National Institute on Alcohol Abuse and Alcoholism publications are available at <http://www.niaaa.nih.gov/Publications>:

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

A Pocket Guide for Alcohol Screening and Brief Intervention

Medical Management Treatment Manual: A Clinical Research Guide for Medically Trained Clinicians Providing Pharmacotherapy as Part of the Treatment for Alcohol Dependence