Medication Assisted Treatment Educational Guideline
Table of Contents

Why Use Medications To Treat Alcohol Dependence

When implemented according to recommended guidelines, medication-assisted treatment combined with brief intervention or more intensive levels of nonpharmacologic treatment can do the following:

- Reduce post-acute withdrawal symptoms that can lead to a return to drinking (e.g., acamprosate's hypothesized mechanisms of action)
- Lessen craving and urges to drink or use drugs (e.g., naltrexone)
- Decrease impulsive or situational use of alcohol (e.g., disulfiram)

Maintaining a therapeutic alliance with a healthcare practitioner can achieve the following:

- Improve patients' attitudes toward change and enhance motivation
- Improve self-esteem and functioning in all aspects of life: employment, familial
- Facilitate treatment adherence, including participation in specialty substance abuse care and support groups

When medications should be considered for treating an alcohol use disorder

- To address 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.

Good candidates:

- Highly motivated for recovery yet considered to be at high risk of relapse to opiate or alcohol abuse.
- Those who have relapse chronically despite multiple treatment episodes.
- Those who live, work or spend time around others with addiction problems
- Those dealing with a high level of personal stress such as job loss, marital problems, etc
- Those that have a tremendous amount to lose by relapsing, such as those with legal consequences to future relapses, job-related monitoring of their progress or threat of loss of spouse or support network
- Those that have failed opiate substitution therapy- would recommend Vivitrol
- Those in their early 20s or teens who have not had the opportunity to establish a strong recovery network through formal addiction treatment and peer support

Initial Assessment – involves Multiple Components of the Client's Life (Medical)

- Evaluation can identify or rule out contraindications to therapy with specific medications
- At the very least, considering a patient's pharmacologic treatment for alcohol dependence should include a physical exam; order laboratory tests; assess psychiatric status; obtain substance use, treatment, and social histories; and assess motivation for change
- In addition to helping healthcare practitioners assess a patient's overall health status, initial laboratory testing can identify the presence of AUDs, alcohol-related damage, and contraindications for use of particular medications
- Several laboratory tests help healthcare practitioners establish a patient's overall health status as well as identify alcohol-related damage and contraindications for using certain medications.

1) ***Complete blood count***. Alcohol overuse causes anemia and has direct toxic effects on bone marrow. An assessment of hematologic laboratory indices is essential when considering pharmacologic treatment of AUDs. Many persons who are alcohol dependent have macrocytosis, and the mean corpuscular volume is often elevated.

2) ***Testing for vitamin deficiencies***

3) ***Hepatic and renal testing***- specifically naltrexone and disulfiram should be used with caution in clients with liver disease and naltrexone and acamprosate should be used with caution in clients with renal (kidney) impairment.

4) ***Pregnancy***- women of childbearing age should receive a pregnancy test before pharmacotherapy is initiated

Initial Assessment (Psychiatric)

- Untreated psychiatric conditions can seriously interfere with a patient's ability to comply with pharmacotherapy and psychosocial treatment for alcohol dependence and can cause the patient preventable suffering

Initial Assessment (Substance Abuse)

- During the assessment, providers should assess the quantity and frequency of alcohol consumption, patterns of alcohol consumption (e.g., persistent, occasional, binge use), episodes of use, duration of use, and consequences of alcohol consumption.

- The history also should include use of substances other than alcohol, especially opioids, as well as the patient's history of use, misuse, or abuse of prescription medications. Misuse of opioid medications may complicate or contraindicate treatment with naltrexone

- Complete assessment includes a patient's current involvement in or history of professional treatment or mutual-help group involvement, including the following:
  1. Detoxification episodes
  2. Pharmacotherapy interventions
  3. Specialty substance abuse treatment episodes (including when, where, modality, duration, and outcome)
  4. Individual therapy
  5. 12-Step (e.g., Alcoholics Anonymous) or other mutual- or self-help program involvement

Initial Assessment (Social History)

- Understanding a patient's social situation identifies problems that may interfere with treatment and that necessitate referral for ancillary services.
- Asking a patient basic questions about his or her work, legal, living, and family situations can yield information that is critical to treatment planning:
  1. What is the patient's family situation? Who should be included in treatment planning? Who can monitor a patient's medication compliance?
  2. Is the patient on probation at work? Could this be a means of motivating medication compliance?
  3. What is the patient's living situation? Are extra measures required to ensure medication compliance? Are psychosocial treatment modalities recommended?

Assessing Motivation for Change

- Before offering treatment for alcohol dependence, providers should assess patients' readiness to change drinking behavior. Through this assessment, patients and providers develop mutually agreeable intervention and treatment plans. Also to be considered:
    1. Past experience with particular maintenance medications
    2. Opinion about which medication may be most helpful
    3. Level of motivation for abstinence
    4. Medical status and contraindications for each medication
    5. History of medication compliance

Questions To Assess Patients' Readiness for Change

- In what ways are you concerned about your drinking
- How much does this concern you
- What are the reasons you see for making a change
- How do you feel about changing 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

Combination Therapy

- A number of studies have found that treatment outcomes improve when naltrexone is combined with acamprosate or disulfiram, particularly for patients who responded poorly to therapy with any of these medications alone.

AUD Medication Decision Grid				
Pretreatment indicators	**Acamprosate (Campral)**	**Disulfiram (Antabuse)**	**Oral Naltrexone (ReVia, Depade)**	**Injectable Naltrexone (Vivitrol)**
Renal Failure	X	A	A	A
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
Unwilling or unable to sustain total abstinence	A	X	A	A
Risk factors for poor med adherence	C	C	C	A
Diabetes	A	C	A	A
Obesity that precludes IM injection	A	A	A	X
Family history of AUDs	A	A	+	+
Bleeding/other coagulation disorders	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 **X=Contraindicated** **C=Use with caution** **+= Particularly appropriate**

Comparison of Approved Medications for Maintenance of Abstinence From Alcohol*

	Acamprosate	**Disulfiram**	**Oral Naltrexone**	**Extended-Release Injectable Naltrexone**
Mechanism of action	Not clearly understood; appears to restore to normal the altered balance of neuronal excitation and inhibition induced by chronic alcohol exposure, possibly through interaction with the glutamate neurotransmitter system	Inhibits aldehyde dehydrogenase, causing a reaction of flushing, sweating, nausea, and tachycardia when alcohol is ingested	Not clearly understood; opioid antagonist; blocks the effects of endogenous opioid peptides; appears to attenuate euphoria associated with alcohol use; may make alcohol use less rewarding; may reduce craving	Same as oral naltrexone
Examples of drug interactions	No clinically relevant interactions alcohol;anticoagulants such as warfarin; amytripyline; isoniazid; diazepam	Metronidazole; Medications containing antidiarrheal medications; thioridazine; yohimbine	Opioid medications; cough/cold medications;	Presumed same as oral naltrexone
Common side effects	Diarrhea and somnolence	Transient mild drowsiness metallic taste; dermatitis; headache; impotence	Nausea; vomiting; anxiety; headache; dizziness; fatigue; somnolence	Same as oral naltrexone plus injection site reactions; joint pain; muscle aches or cramps
Contra-indications	Severe renal impairment (creatinine clearance ≤ 30 mL/min)	Hypersensitivity to rubber derivatives; significant liver disease; alcohol still in system; coronary artery disease	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; body mass that precludes deep intramuscular injection; rash or infection at injection site
Cautions	Dosage may be modified for moderate renal impairment (creatinine clearance 30–50 mL/ min); pregnancy category C†	Hepatic cirrhosis or insufficiency; cerebrovascular disease; psychoses; diabetes mellitus; epilepsy; renal impairment; pregnancy category C†	Renal impairment; chronic pain; pregnancy category C†	Same as oral naltrexone, plus hemophilia or other bleeding problems

Serious adverse reactions	Rare events include suicidal ideation; severe persistent diarrhea	Disulfiram–alcohol reaction; hepatotoxicity peripheral neuropathy; psychotic reactions; optic neuritis	Precipitates opioid withdrawal if the patient is dependent on opioids; hepatotoxicity (although it does not appear to be a hepatotoxin at recommended doses)	Same as oral naltrexone plus inadvertent subcutaneous injection may cause a severe injection-site reaction; depression; rare events including allergic pneumonia and suicidal ideation and behavior

Acomprosate

Acamprosate's action in maintenance of alcohol abstinence is not completely understood, but evidence indicates that acamprosate interacts with the glutamate neurotransmitter system, reducing and normalizing the pathologic glutamatergic hyperactivity that occurs during protracted withdrawal from alcohol. It is hypothesized that this normalization leads to a reduction of common symptoms of protracted, or postacute, withdrawal such as insomnia, anxiety, and restless-ness—symptoms that may contribute to a patient's return to alcohol use

Safety

Acamprosate has a good safety profile:

- Patients maintained on acamprosate have not developed tolerance for or dependence on it and it appears to have no potential for abuse.
- It carries virtually no overdose risk; even at overdoses up to 56 grams (a normal daily dose is 2 grams), acamprosate was generally well tolerated by patients (Thomson Healthcare, Inc., 2006).
- Most side effects are mild and transient, lessening or disappearing within the first few weeks of treatment (diarrhea tends to persist).
- Although there is a pharmacokinetic interaction by which acamprosate can increase naltrexone blood levels, there are no other clinically significant interactions between acamprosate and other medications (Johnson et al., 2003).

Acamprosate also has advantages over other medications for treating AUDs in some patients:

- Because acamprosate is not metabolized by the liver, it can be used safely even by patients with severe liver disease, unlike oral or injectable naltrexone or disulfiram.
- Because it does not affect endogenous or exogenous opioids, it can be used with patients receiving opioid maintenance therapy (reviewed by Myrick & Anton, 2004) or undergoing treatment with opioids for acute or chronic pain, unlike oral or injectable naltrexone.
- Because acamprosate does not interact with benzodiazepines or other medications used in medical detoxification, it can be continued safely if a patient returns to drinking and subsequently requires detoxification.
- Because there are no clinically significant drug interactions with acamprosate, it can be a safe medication for patients who are coping with multiple medical issues and are taking many other medications.

Initiating Treatment With Acamprosate

Acamprosate is typically initiated 5 days following drinking cessation. However, acamprosate can be used safely with alcohol (and with benzodiazepines), and it ***can*** be started during medically supervised withdrawal. Acamprosate therapy should be maintained if a patient relapses to alcohol use. Acamprosate reaches full effectiveness in 5 to 8 days. Research on patient-specific characteristics as predictors of acamprosate efficacy has not identified any particular characteristics (e.g., level of physiological dependence on alcohol, age of onset, gender) that predict acamprosate treatment outcomes.

Before initiating treatment (acomprosate), healthcare practitioners should do the following:

- Conduct or refer patients for 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.

The benefits and limitations of acamprosate - What to expect

- Possible side effects
- Full effectiveness in 5–8 days
- For women of childbearing age, the importance of using an effective birth control method
- To continue taking acamprosate if a slip or relapse occurs and to inform their prescribing professional immediately
- To notify the prescribing professional immediately if they begin to have suicidal thoughts, if they begin to feel depressed, or if an existing depression worsens
- That tablets should not be crushed
- Not to take extra medication if a dose is missed and it is time to take the next dose.

Treatment Duration and Discontinuing Acamprosate

- The length of time a particular patient takes acamprosate will be determined, ideally, with input from the prescribing professional, the specialty treatment provider, and the patient
- Discontinuation of acamprosate may be considered once a patient has achieved stable abstinence from alcohol, reports diminished craving, and has established a sound plan and support for ongoing recovery.
- There is no withdrawal syndrome associated with discontinuing acamprosate, and it is not necessary to taper the dose.

Acamprosate Side Effects	
Most Common Side Effect	**Less Common Side Effects**
Diarrhea	Suicidal ideation (less common, but serious) Intestinal cramps Headache Flatulence Itchiness Dizziness Increased or decreased libido Insomnia Anxiety Muscle weakness Nausea

Acamprosate Contraindications	
Patient Condition or Circumstance	**Treatment Recommendation**
Previous hypersensitivity Severe renal impairment (Creatinine clearance) < 30mL/min)	Do not prescribe acamprosate
Pregnant or nursing women	Avoid using acamprosate unless potential benefits outweigh risks (Acamprosate is FDA pregnancy category C; it is unknown whether acamprosate is excreted in human milk.)
Moderate renal impairment (creatinine clearance 30–50 mL/min)	Reduce dosage to one 333 mg tablet daily
Children or adolescents	Prescribe with caution; acamprosate has not been evaluated for safety or efficacy in pediatric or adolescent populations

Disulfiram (Antabuse)

Disulfiram was the first medication approved by the U.S. Food and Drug Administration (FDA) to treat chronic alcohol dependence. In its pure state, disulfiram is a white to off-white, odorless, almost tasteless powder, which is soluble in water and alcohol. Disulfiram, an alcohol-aversive or alcohol-sensitizing agent, causes an acutely toxic physical reaction when mixed with alcohol. Continuing research and clinical findings have clarified disulfiram's mode of action and established its safe and effective use in the treatment of alcohol use disorders (AUDs) in some patient groups.

Aversive treatment

Unlike other medications approved to treat alcohol dependence disulfiram does not affect brain opiate, g-aminobutyricacid, or glutamate receptors directly.
Whether disulfiram directly decreases the urge to drink remains uncertain. However, disulfiram definitely disrupts the metabolism of alcohol, causing a severe reaction when patients mix disulfiram and alcohol.

The disulfiram–alcohol reaction

The disulfiram–alcohol reaction usually begins about 10 to 30 minutes after alcohol is ingested.
It can take up to 2 weeks for the body to synthesize sufficient unbound enzyme to metabolize alcohol adequately. This is why alcohol ingestion may produce unpleasant symptoms for up to 2 weeks after a patient has taken the last dose of disulfiram.

Body Part Affected	Moderate	Severe
Body skin	Sweating Warmth and flushing, particularly on upper chest and face	None
Respiratory system	Hyperventilation Respiratory difficulty/dyspnea	Respiratory depression
Head, neck, throat	Acetaldehyde breath odor Blurred vision Head and neck throbbing Thirst	None
Stomach, digestive system	Nausea/vomiting	None
Chest, heart, circulatory system	Chest pain/palpitations Hypotension Tachycardia	Cardiovascular collapse Arrhythmia Myocardial infarction (in individuals with preexisting coronary artery disease) Acute congestive heart failure (in individuals with preexisting myocardial dysfunction)
Brain/nervous system	Vertigo Syncope Marked uneasiness Confusion	Seizures
Other	Weakness	Death

How Is Disulfiram Used

Physicians should not administer disulfiram until the following steps have been taken:

- Educate the patient about disulfiram and obtain informed consent.

- Wait until the patient has abstained from alcohol at least 12 hours and/or breath or blood alcohol level is zero.
- Perform a physical exam, baseline liver and kidney function tests, and a pregnancy test for women.
  Perform an electrocardiogram if clinically indicated (e.g., history of heart disease).
- Complete a medical and psychiatric history. Determine allergies to disulfiram or other drugs; prescription and nonprescription medications taken, including vitamins; history of cardiovascular disease, diabetes, thyroid disease, seizure disorder, central nervous system impairment, or kidney or liver disease; and for women, reproductive status, including current pregnancy or plans to become pregnant or to breast-feed.

Supervised Ingestion

There is strong evidence that supervised ingestion is necessary for disulfiram therapy compliance (e.g., Brewer et al., 2000; Kristenson, 1995; reviewed by Fuller & Gordis, 2004). Although not absolutely essential, supervised administration by a pharmacist, healthcare provider, or family member is preferred as a key component of the treatment plan.

Disulfiram Side Effects

Skin/acneiform eruptions	Headache	Allergic dermatitis
Mild drowsiness	Fatigue	Metallic or garlic- like aftertaste

*Dermatologic side effects often can be managed with concomitant antihistamines.

Disulfiram Contraindications	
Patient Condition or Circumstance	**Treatment Recommendation**
Known hypersensitivity to disulfiram or other thiuram derivatives used in pesticides and rubber vulcanization; sulfur or nickel allergy	Do not administer disulfiram.
Psychosis	Disulfiram is relatively contraindicated in patients with decompensated psychoses but can be used with caution in treated, stable patients with schizophrenia or other psychotic disorders.
Severe myocardial disease and/or coronary occlusion	Disulfiram is relatively contraindicated in patients with severe myocardial disease or coronary occlusion, with clinical risk of disulfiram therapy balanced against clinical risk of ongoing alcohol abuse. Perform an electrocardiogram before and during disulfiram therapy and follow closely.
Pregnant or nursing women	Although disulfiram is not absolutely contraindicated, it should be avoided because risk to the fetus is unknown. (Pregnant patients should receive behavioral treatment, on an inpatient basis if necessary.) Do not give disulfiram to nursing mothers. Patients should discontinue nursing before taking disulfiram.

Disulfiram Cautions	
Patient Condition or Circumstance	**Treatment Recommendation**
History of cardiac disease, diabetes mellitus, hypothyroidism, epilepsy, cerebral damage, chronic or acute nephritis, hepatic cirrhosis, or hepatic insufficiency	Use with caution. No evidence exists that patients with preexisting liver disease are more likely to suffer severe hepatotoxicity from disulfiram therapy.
Patients with hepatitis C	According to current available evidence, if baseline transaminase levels are normal or only moderately elevated (less than five times the upper limit of normal), use with careful monitoring of liver function.
Children and adolescents	Safety and efficacy for children has not been determined. One study indicates that disulfiram can be safe and effective with adolescents (Niederhofer & Staffen, 2003). Administer with caution.
Patients receiving or who have recently received metronidazole, paraldehyde, alcohol, or alcohol-containing preparations (e.g., cough syrups, tonics); also patients exposed to ethylene dibromide or its vapors (e.g., in paint, paint thinner, varnish, shellac)	Do not use disulfiram until substances are out of the patient's system.
Patients using products that contain alcohol in disguised forms (e.g., vinegars, sauces, aftershave lotions, liniments)	Instruct patients to test any alcohol-containing product before using it by applying some to a small area of the skin for 1 to 2 hours. If there is no redness, itching, or unwanted effects, the product may be used safely
Age 61 or older	Age 61 or older

Managing a disulfiram–alcohol reaction

The duration of the disulfiram–alcohol reaction varies from 30 to 60 minutes in mild cases to several hours or until the alcohol is metabolized in more severe cases. When effects are severe, supportive measures may be needed to restore blood pressure and treat shock. Administration of oxygen or carbogen, large intravenous doses of vitamin C (1 g), ephedrine sulfate, or intravenous antihistamines may be indicated. Potassium levels should be monitored particularly in patients on digitalis because hypokalemia has been reported.

Patient Education

In addition to giving patients the general patient education healthcare providers should educate patients about the following key points regarding disulfiram therapy:

- Benefits and limitations of disulfiram
- What to expect from disulfiram and normal time to full effect
- Complete information about the disulfiram–alcohol reaction
- Strong cautions about surreptitious drinking while on disulfiram
- Warnings about using alcohol in disguised forms, such as in sauces, vinegars, cough mixtures, aftershave lotions, or liniments

- Importance of continued counseling and 12-Step or mutual-help group participation during disulfiram therapy
- Importance of informing the counselor and prescribing professional if a slip or relapse occurs
- Importance of telling physicians or dentists that the patient is taking disulfiram when he or she is scheduled for surgery, including dental surgery
- Importance of carrying a safety identification card indicating that the patient is taking disulfiram, symptoms of possible disulfiram–alcohol reactions, and the physician or institution to contact in an emergency
- Symptoms of potential neurologic injury to report immediately to the physician
- Symptoms of potential liver injury to report immediately to the physician.

Drug Interactions With Disulfiram

Drug	Effect With Disulfiram	Recommended Action
Benzodiazepines Chlordiazepoxide (Librium®) Diazepam (Valium®)	Decreases plasma clearance of chlordiazepoxide or diazepam	Substitute oxazepam (Serax®) or lorazepam (Ativan®)
Isoniazid	May cause unsteady gait, changes in mental state	Discontinue disulfiram if either effect is noted
Rifampin (Rifidin® , Rimactane®)	If used with isoniazid to treat tuberculosis, see isoniazid effects above	Adjust dosages as needed
Metronidazole (Flagyl®)	Leads to a greater likelihood of confusion or psychosis	Do not prescribe disulfiram and metronidazole concomitantly
Oral anticoagulant (e.g., warfarin [Coumadin®])	Inhibits warfarin metabolism	Adjust dosages as needed
Oral hypoglycemic	Produces disulfiram-like reactions with alcohol	Monitor carefully if prescribing oral hypoglycemics and disulfiram concomitantly
Phenytoin (Dilantin®)	Increases serum levels through CYP 450 2C9 inhibition	Obtain baseline phenytoin serum level before disulfiram therapy; reevaluate level during therapy; adjust dosage if phenytoin level increases
Theophylline	Increases serum levels through CYP 450 1A2 inhibition	Obtain baseline theophylline serum level before disulfiram therapy; reevaluate level during therapy; adjust dosage if theophylline serum level increases
Tricyclic antidepressants, amitriptyline (Elavil®)	May cause delirium with concurrent administration	Adjust dosages, discontinue disulfiram, or switch to another class of antidepressant medication
Desipramine (Norpramin®), imipramine (Tofranil®)	Decreases total body clearance and increases elimination half-life and peak plasma levels of desipramine or imipramine	Monitor closely; adjust dosages if needed

Laboratory Testing in Disulfiram Therapy	
Interval/Period	**Type of Test**
Before starting disulfiram therapy to confirm abstinence and determine baselines after stabilization	Breath or blood alcohol tests (if clinically indicated to confirm abstinence) Liver function tests: Alanine aminotransferase, aspartate aminotransferase, gamma glutamyltransferase, alkaline phosphatase, lactate dehydrogenase, bilirubin, total protein, albumin, prothrombin time Complete blood count, routine chemistries (if clinically indicated) Kidney function tests: Routine blood urea nitrogen (BUN), creatinine Pregnancy test (women of childbearing age)
10–14 days after initiation of therapy and then monthly (or more frequently) for first 6 months of therapy; every 3 months thereafter	Liver function tests: Alanine aminotransferase, aspartate aminotransferase, gamma glutamyltransferase, bilirubin
Monthly during therapy	Pregnancy test (women of childbearing age)
As clinically indicated during therapy	Kidney function tests: BUN, creatinine Urine toxicology screen: Perform only when concern exists about unreported alcohol or drug use

Oral Naltrexone

Naltrexone hydrochloride is a relatively pure and long-lasting opioid antagonist. Oral naltrexone has been used to treat opioid dependence for many years and has been approved to treat alcohol use disorders (AUDs) since 1994. Naltrexone reduces both the rewarding effects of alcohol and craving for it. Peak naltrexone plasma concentrations are reached within 1 hour of dosing and has an elimination half-life of 13 hours. Naltrexone achieves therapeutic effectiveness rapidly following the initiation of oral dosing.

Why Use Oral Naltrexone

Naltrexone appears to be effective for attenuating craving in people who are alcohol dependent (Monti et al., 1999, 2001). By blocking craving, naltrexone may enhance the ability of patients to abstain from drinking. By blocking the pleasure from alcohol, naltrexone also may reduce the amount of heavy drinking in those who do drink. Naltrexone may afford people with AUDs a measure of control that can prevent a slip from becoming a full-blown relapse.

Safety

Naltrexone has a low incidence of common adverse events. Naltrexone's FDA-approved label includes a black-box warning regarding hepatotoxicity, although these reversible effects tend to be associated with much higher doses than those used in routine clinical practice (e.g., 300 mg/day or more) and tend to occur only after a patient is on these high doses for extended periods. As an opioid antagonist, naltrexone competitively displaces opioid medications from their binding sites, precipitating withdrawal. Healthcare providers must ensure that patients have been fully withdrawn from all opioids before considering therapy with naltrexone.

Initiating Treatment With Oral Naltrexone

FDA labeling recommends that treatment with naltrexone not begin until signs and symptoms of acute alcohol withdrawal have 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 begin treatment with naltrexone. However, it is safe for patients to begin taking naltrexone during medically supervised withdrawal or if they are actively drinking.

Before initiating treatment with naltrexone, healthcare practitioners should do the following:

- Conduct a medical evaluation that includes a physical exam, psychosocial assessment, and laboratory testing, including toxicological screening and liver function testing to establish suitability for medication and to establish a baseline for comparison
- Discuss the risks of naltrexone use during pregnancy and advise women of childbearing age to use birth control while taking naltrexone
- Ensure that patients are not regular users of opioids (illicit drugs, opioid maintenance medications, or opioid pain medications) to avoid precipitating withdrawal
- Strongly caution patients of the unpleasant physical effects of opioid withdrawal that will result if patients are not completely detoxified from opioids.

Monitoring Oral Naltrexone

It is important that either the patient be highly motivated for treatment or a medication monitoring plan be used to encourage naltrexone use if the patient is not highly motivated.

To maximize compliance, physicians should observe dosing or encourage a family member or significant others to monitor medication use, especially at the beginning of treatment with naltrexone.

Strategies such as incentives and feedback on medication compliance have been incorporated into treatment planning to enhance compliance. After the patient's motivation has increased and he or she feels better and stronger, medication monitoring may no longer be needed.

Patients With Intense Alcohol Craving

Patients with intense alcohol cravings during treatment may experience greater medication benefit than patients with low levels of alcohol craving (Monterosso et al., 2001).

Also, patients with more somatic complaints may have better outcomes when treated with naltrexone compared with patients with less physical distress.

Both human laboratory studies and clinical trials have suggested that patients with a family history of alcohol dependence may benefit more from naltrexone treatment than patients without a family history of alcohol dependence (Monterosso et al., 2001; Rubio et al., 2005).

Treatment Duration and Discontinuing Oral Naltrexone

1. The FDA label states that naltrexone should be taken for up to 3 months to treat AUDs.
2. Healthcare providers should tailor the length of treatment to individual patients. Naltrexone has been administered to patients who are alcohol dependent for 6 months to 1 year with no additional safety concerns (Balldin et al., 2003; O'Malley et al., 2003).
3. Because of naltrexone's efficacy in reducing the rewarding effects of alcohol consumption (McCaul, Wand, Eissenberg, Rohde, & Cheskin, 2000) and reducing cravings for alcohol (O'Malley et al., 1992), patients who achieve abstinence may benefit from taking naltrexone at times when they are at higher risk of relapse, such as on vacations, on holidays, or during a personal tragedy.
4. Discontinuation of oral naltrexone is not associated with a withdrawal syndrome, and it is not necessary to taper the dose. Providers should remind patients that they should not take opioid medications for at least 3 days and that they may be more sensitive to the effects of opioid drugs

Oral Naltrexone Dosages	
Initial dosage for most patients	50 mg/day in a single tablet
Initial dosage for patients at risk of adverse events (e.g., women, younger patients, those with shorter abstinence)	12.5 mg/day (quarter tablet) or 25 mg/ day (half tablet) for 1 week, taken with food (2 weeks, if necessary); gradually increase to 50 mg/day
Average maintenance dosage	50 mg/day

Oral Naltrexone Side Effects	
Most Common	**Less Common**
Nausea Vomiting Headache Dizziness Fatigue Nervousness Anxiety Somnolence	Diarrhea, constipation, stomach pains, cramps Chest pain, joint/muscle pain Rash Difficulty sleeping Excessive thirst, loss of appetite Sweating Increased tears Mild depression Delayed ejaculation

Naltrexone Contraindications	
Patient Condition or Circumstance	**Treatment Recommendation**
Current illicit opioid use (as indicated by self-report or a positive urine screen) or buprenorphine (Suboxone® or Subutex®) or methadone maintenance therapy for the treatment of opioid dependence; currently undergoing opioid withdrawal	Do not prescribe oral naltrexone; consider an alternative medication
Acute hepatitis or liver failure	Do not prescribe oral naltrexone
Anticipated need for opioid analgesics within the next 7 days	Do not prescribe oral naltrexone
History of sensitivity to naltrexone, to structurally similar compounds (e.g., naloxone or nalmefene), or to any inactive ingredients in the tablet	Do not prescribe oral naltrexone

Naltrexone Cautions **Patient Condition or Circumstance**	**Treatment Recommendation**
Active liver disease	Monitor liver function frequently
Moderate to severe renal impairment	Use with careful monitoring (naltrexone is eliminated through the kidneys)
Pregnant and nursing women	Do not prescribe during pregnancy and nursing unless potential benefits outweigh risks (oral naltrexone is FDA pregnancy category C; it is unknown whether oral naltrexone is excreted in human milk)
Women of childbearing age	Caution patients that effects on fetus are unknown and encourage use of an effective birth control method
Serum aminotransferase levels greater than 5 times the upper limit of normal	Generally avoid, unless potential benefits outweigh risks
Chronic pain syndromes; acute or recurring need for opioid analgesics	Have patients abstain from naltrexone for at least 3 days (conservatively, 7 days) before initiating opioid analgesics

Adverse Reactions to Naltrexone and Their Management	
Adverse Reaction	**Management**
Nausea	Suggest that the patient take naltrexone with complex carbohydrates (e.g., bread) rather than on an empty stomach Suggest that the patient take naltrexone with a tablespoon of simethicone (e.g., Gas-X® and Mylicon®) or bismuth subsalicylate (e.g., Pepto-Bismol®) Reduce dose or cease for 3 or 4 days and reinitiate at lower dose
Liver toxicity	Discontinue naltrexone
Precipitated opioid withdrawal	Discontinue further doses of naltrexone Provide supportive treatments (i.e., hydration and antispasmodic and antidiarrheal medications) until opioid withdrawal symptoms resolve Provide α-2-agonists such as clonidine to mitigate some withdrawal symptoms; watch for enhanced side effects of clonidine, including dizziness, hypotension, fatigue, and headache
Naltrexone overdose	Treat symptomatically under close supervision Contact poison control for most recent information

Drug Interactions With Oral Naltrexone	
Drug	**Effect With Oral Naltrexone**
Cough/cold medications	May decrease benefit if medication contains an opioid
Antidiarrheal medications	May block benefit if medication contains an opioid
Opioid analgesics	May require greater amount of analgesic than usual and may result in deeper and more prolonged respiratory depression than if the patient were not taking naltrexone
Thioridazine	May result in lethargy and somnolence
Yohimbine	May result in anxiety and increased pulse and blood pressure
Nonsteroidal anti-inflammatory drugs (NSAIDs)	May result in liver enzyme elevations (i.e., aspartate aminotransferase [AST] and alanine aminotransferase [ALT]) in combination with regular use of very high doses of naltrexone (200–250 mg/day) (Kim, Grant, Adson, & Remmel, 2001); this effect has not been observed in the recommended therapeutic dose range of naltrexone (50–100 mg)

Extended-Release Injectable Naltrexone (Vivitrol)

Extended-release injectable naltrexone is a microsphere formulation of the opioid antagonist (blocker) medication naltrexone. It is administered by intramuscular (IM) gluteal injection once a month. The extended-release injectable form helps address patient noncompliance, which can limit the effectiveness of oral naltrexone

Pharmacology

The injectable naltrexone plasma concentration peaks approximately 2 hours after IM injection followed by a second peak approximately 2 to 3 days later.

Beginning approximately 7 days after dosing, plasma concentrations slowly decline, maintaining a therapeutic naltrexone blood level over 4 weeks and avoiding daily peaks and troughs that occur with oral naltrexone. Steady state is reached at the end of the dosing interval following the first injection.

Unlike oral naltrexone, injectable naltrexone does not undergo first-pass metabolism in the liver. As a consequence, the total monthly dose of naltrexone administered is considerably less for extended-released (380 mg) compared with oral naltrexone (1,500 mg). Therefore, the peak concentration of the drug to which the liver is exposed is substantially less for injectable naltrexone than for oral naltrexone. Because naltrexone-induced hepatotoxicity is dose dependent, injectable naltrexone would be expected to show less hepatotoxicity than the oral form.

Naltrexone is an opioid antagonist, so individuals who are opioid dependent may experience opioid withdrawal. Treatment with injectable naltrexone should not be initiated unless the patient is 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.

How Is Extended-Release Injectable Naltrexone Used

Treatment with injectable naltrexone should be part of a management program that provides patient education, addresses the psychological and social problems of patients, and encourages attendance at 12-Step or mutual-help meetings or other community support.

For *optimal* results with injectable naltrexone, candidates for treatment should meet several criteria:

- They must be medically appropriate to receive naltrexone.
- They should not be using opioids currently or have evidence of recent use.
- They should not be anticipating surgery or have a condition, such as chronic pain, for which opioid analgesics may be required in the future.
- They should not have severe liver or kidney disease, although naltrexone can be used cautiously in persons with mild to moderate hepatic impairment or mild renal insufficiency.
- They should not have a condition, such as a bleeding disorder or obesity, which prevents them from receiving a deep IM injection.
- They should have been abstinent for at least 4 days.
- They should be motivated to maintain abstinence or to reduce their drinking.
- They should be willing to participate in psychosocial substance abuse treatment such as counseling and support groups.

Possible Target Patients

- Include those who are ***unable*** to maintain medication adherence for some reason (e.g., poor memory)
- Those who would prefer not to have the burden of remembering to take medication daily.

Because injectable naltrexone is the newest form of a medication for the treatment of AUDs, the optimal situations for its use remain to be defined. However, it combines two attractive features: a medication for which there is substantial evidence for efficacy and a delivery system that eliminates daily medication compliance. As such, it represents an important addition to the list of medications for the treatment of alcohol dependence.

Before initiating treatment with injectable naltrexone, healthcare practitioners should do the following:

1. Conduct a physical examination
2. Determine liver function (alanine aminotransferase [ALT], aspartate aminotransferase [AST], gamma glutamyltransferase [GGT], and bilirubin)
3. Obtain toxicological screening tests.

Patients being maintained on buprenorphine (Suboxone or Subutex) or methadone for the treatment of opioid dependence cannot undergo treatment with naltrexone.

Overdose **should not** be a concern for patients receiving injectable naltrexone because it is unlikely that patients will receive more than one IM injection per month.

Treatment Duration and Discontinuing Extended-Release Injectable Naltrexone

Research has not yet clearly defined the optimal duration of treatment with injectable naltrexone.

Healthcare providers may consider discontinuing injectable naltrexone once a patient has achieved stable abstinence from alcohol and has established a sound plan and support for ongoing recovery or if a patient is not compliant with the medication regimen.

Like oral naltrexone, injectable naltrexone may be useful for short periods when a patient in stable recovery is at particular risk for relapse to problem alcohol use.

Patients discontinuing injectable naltrexone should be reminded that they should not take any opioid medications for ***at least*** **30** days from the date of their last injection. Patients also should be warned that after discontinuing treatment they may be more sensitive to the effects of opioid drugs

Before administering injectable naltrexone, physicians should advise patients of the unpleasant physical effects of opioid withdrawal that will result if patients are not completely detoxified from opioids. Injectable naltrexone is available through specialty pharmacies.

Extended-Release Injectable Naltrexone Side Effects
Injection site reactions Fatigue (sometimes severe)
Back pain Nausea
Upper abdominal Vomiting pain Headache Decreased appetite Dizziness

Extended-Release Injectable Naltrexone Contraindications	
Patient Condition or Circumstance	**Treatment Recommendation**
History of sensitivity to PLG, carboxymethylcellulose, or any components of the diluent	Do not administer injectable naltrexone
Anticipated need for opioid analgesics within the next 30 days	Do not administer injectable naltrexone
Patient obesity	Do not administer injectable naltrexone if patient's body mass precludes IM injection with the provided 1.5inch needle Inadvertent subcutaneous injection may cause a severe injection-site reaction

Extended-Release Injectable Naltrexone Cautions	
Patient Condition or Circumstance	**Treatment Recommendation**
Thrombocytopenia or coagulation disorders	Monitor carefully for 24 hours after injection
Recent opioid dependence	Explain to the patient the risk of precipitated withdrawal if the patient has used opioids recently Explain to the patient that the opioid-blocking effects last for at least 30 days and that the risks associated with a return to opioid use are significant

Patient Education

- Once naltrexone is injected, it is impossible to remove it from the body; if problems occur, the effects can last up to 30 days.
- The onset of naltrexone's effects will probably occur within several hours although full effectiveness may not occur for 2 to 3 days following first injection. The duration of the effects appears to be 30 days.
- Injectable naltrexone blocks the effects of opioids and opioid like drugs (e.g., heroin, opioid analgesics, opioid-based antidiarrheals, and antitussives) for up to 30 days, which may complicate the treatment of pain if it occurs during this period. Patients should be assured that other options for analgesia exist.
- Injectable naltrexone blocks low to moderate doses of opioids, but large doses of heroin or other opioids may lead to serious injury, coma, or death. For patients with a history of opioid use, the use of injectable naltrexone may lower tolerance for opioids, resulting in a greater sensitivity to lower doses of opioids after injectable naltrexone treatment is discontinued; this increased sensitivity could result in overdose and respiratory depression.
- Injectable naltrexone is more likely to reduce drinking if it is used in conjunction with psychosocial interventions, such as specialized substance abuse treatment and community supports (e.g., counseling, 12-Step, or other mutual-help groups).
- Patients should carry a safety ID card that indicates they are taking injectable naltrexone.

Integrating Medication for Alcohol Dependence Into Clinical Practice Settings

- Pharmacotherapy for alcohol use disorders (AUDs) is underused both in specialized substance abuse treatment programs and in office-based medical practice.
- The consensus panel acknowledges that much resistance to pharmacotherapy exists—from third-party payers, some clinicians, some individuals participating in self-help groups who view medications as substituting a pill for self-empowerment and self-responsibility, and some patients and their families.
- The diagnoses of alcohol dependence and abuse, as well as hazardous alcohol use, continue to carry significant social stigma that affects both the person who is alcohol dependent and healthcare providers. This stigma continues to exist, in part, because of a lack of understanding of alcohol dependence as a treatable medical disorder.
- Providers often worry that persons who are alcohol dependent have complicated conditions that take too much time to treat.

Choosing a Medication

1. Past experience with particular maintenance medications
2. Opinion about which medication may be most helpful
3. Level of motivation for abstinence
4. Medical status and contraindications for each medication
5. History of medication compliance

Elements of Patient Education

- Information about alcohol dependence as a chronic medical disorder
- Description of what to expect in recovery, including symptoms of post-acute withdrawal
- List of the possible benefits of a particular medication

- Information about the medication itself:
  - How and when to take it and the importance of complying with the regimen
  - When the medication will become fully effective
  - Possible common side effects and their expected duration
  - Under what conditions the patient should immediately call the provider
  - Any cautions regarding daily activities
  - Medication interactions

- Explanation of the importance for women of childbearing age to use an effective birth control method
- Information about what to do if the patient starts drinking after a period of abstinence
- Description of the importance of concurrent psychosocial treatment and mutual- or self-help programs

Follow-up plans.

- Specific patient education unique to each medication is in the medication listed under each medication in this guide.

Monitoring Cravings

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

Patients should be asked about current craving as well as how they felt 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).

Patients may be asked whether any episodes have caused particular problems for them.

The patterns of craving over time can be useful. Both the provider and the patient can see that the patient's patterns of craving may fluctuate throughout the day and over longer periods; these patterns can assess the appropriateness to continue, adjust, supplement, enhance, or terminate pharmacologic treatment.

Alcohol Cravings Scale

Level	Description of Craving
10	Even if you tried to stop me I would do anything (steal, prostitute myself, harm others) to drink.
9	Even if you tried to stop me, I would try to leave now and drink
8	I want to leave now and drink. I'm really craving hard.
7	If I were in the community I would try to drink.
6	If someone offered me alcohol I would drink it.
5	If someone offered me my favorite type of alcohol I would drink it.
4	If someone offered me alcohol I might drink.
3	If someone offered me alcohol I might not drink.
2	If someone offered me alcohol I would not drink
1	If someone offered me alcohol I would definitely refuse it and NOT drink.
0	I no longer have any desire to drink. Alcohol is poison. I will NEVER drink again.

Discontinuing Pharmacotherapy

Because an AUD is a chronic disorder, patients may need long-term use of medication or more than one episode of pharmacotherapy.

Some patients may benefit from using a medication over short periods to help them through a particularly stressful period or a situation that has typically elicited cravings for alcohol (e.g., a patient may want to take disulfiram or naltrexone while visiting family members who drink excessively).

Ideally, the patient and provider will decide together to discontinue pharmacotherapy. A patient may simply stop taking the medication. A patient also may express a desire to discontinue a medication because of side effects or for other reasons, or a patient will need to discontinue medication because of significant negative changes in laboratory findings or physical health status.

Otherwise, the patient and provider may consider discontinuing medication under the following conditions:

- The patient reports substantially diminished craving
- The patient has maintained stable abstinence over a sustained period
- The patient feels ready to discontinue the medication
- The patient is engaged in ongoing recovery, including community supports

Drug Cravings Scale

Level	Description of Craving
10	Even if you tried to stop me I would do anything (steal, prostitute myself, harm others) to get high.
9	Even if you tried to stop me, I would try to leave now and get high
8	I want to leave now and get high. I'm really craving hard.
7	If I were in the community I would try to get high.
6	If someone offered me drugs I would get high
5	If someone offered me my favorite type of drug I would get high
4	If someone offered me drugs I might get high.
3	If someone offered me drugs I might not get high.
2	If someone offered me drugs I would not get high.
1	If someone offered me drugs I would definitely refuse it and NOT get high.
0	I no longer have any desire to get high. Drugs are poison. I will NEVER get high again.

American Society of Addiction Medicine

Supplement on Pharmacotherapies for Alcohol Use Disorders

Rational for Pharmacotherapy for Alcohol Use Disorders
The hope is that by using all of the tools at our disposal, we can assist patients to abstinence and then to recovery.

Pharmacologic Approaches to Relapse Prevention
Pharmacotherapies are becoming a standard component of the relapse prevention and management armamentarium. While not indicated for every patient, they are an important component of care for many individuals.

Selecting a Pharmacologic Agent –if indicated:
If a particular medication was helpful or effective in the past, then a repeat trial of the same medication should be considered.
If a particular medication was not helpful or effective in an earlier trial, then the use of a different medication is warranted.

Factors considered in selecting a particular pharmacologic agent

1) If the patient is not motivated for abstinence (a) consider naltrexone or long-acting naltrexone
2) If the risk of relapse is related to the patient's reports of subjective reward or pleasure associated with drinking (positive reinforcement), consider naltrexone or long-acting naltrexone
3) If the risk of relapse is related to the patient's report of relief of discomfort or dysphoria associated with drinking (negative reinforcement), consider acamprosate
4) If the patient reports strong subjective cravings for alcohol, consider naltrexone or long-acting naltrexone.
5) If the patient has a strong family history of alcoholism, consider naltrexone or long-acting naltrexone.

Special Strategies to Enhance Medication Compliance/Adherence
Supervision of medication self-administration or direct administration by a caregiver

Duration of Treatment
The risk of relapse to alcohol dependence is very high in the first 6-12 months after initiating abstinence and gradually diminishes over several years. Therefore, a minimum initial period of 3 months of pharmacotherapy is recommended.
It is reasonable to continue treatment for a year or longer if the patient responds to medication.
Pharmacotherapy may be reinstated if a relapse occurs.