PRESCRIBING PHARMACOTHERAPIES FOR PATIENTS WITH ALCOHOL USE DISORDER

Alcohol is the most widely misused substance in the United States. According to the 2019 National Survey on Drug Use and Health, more than 65 million Americans engaged in recent binge alcohol use and more than 14.5 million were classified as having alcohol use disorder (AUD; Substance Abuse and Mental Health Services Administration, [SAMHSA] 2020a). This is especially concerning given the many physical illnesses associated with alcohol misuse (SAMHSA, 2020c) as well as its contribution to deaths and injuries from car accidents (Centers for Disease Control and Prevention, 2020; National Highway Traffic Safety Administration, n.d.); violence and criminal activity; and riskier sexual behavior, which can lead to higher incidences of sexually transmitted diseases.

Healthcare providers can play a key role in mitigating this public health burden. Currently, there are four U.S. Food and Drug Administration (FDA)-approved medications for treating problematic alcohol use: acamprosate, disulfiram, oral naltrexone, and extended-release injectable naltrexone (XR-NTX). These medications are effective, lack abuse potential, and can be prescribed by any healthcare professional with the appropriate credentials. When used with counseling and other evidence-based techniques, they can help people reduce their drinking levels and achieve abstinence.

This Advisory, based on SAMHSA’s Treatment Improvement Protocol (TIP) 49, Incorporating Alcohol Pharmacotherapies Into Medical Practice, focuses on medication and related treatment decisions made after screening and assessment, and medically supervised withdrawal, if necessary. Alcohol consumption should not stop abruptly in those patients who have consumed alcohol regularly over a prolonged period of time. This Advisory is meant as an overview of AUD medications to facilitate abstinence.

**Key Messages**

- Many people with AUD can benefit from the four FDA-approved medications to treat this condition: acamprosate, disulfiram, oral naltrexone, and XR-NTX.
- Healthcare professionals need to match patients with the appropriate AUD medication. Factors to consider include patient needs, stage of patient’s recovery, preferences, age, and preexisting medical conditions, as well as potential medication interactions.
- Prescribers need to conduct lab tests for each patient. AUD is often accompanied by physical ailments, some of which may be contraindications for a particular medication.
- Healthcare professionals should also incorporate patient education, psychosocial treatment, and patient monitoring into care. When to discontinue treatment is an equally important clinical decision.
Medication Overview

<table>
<thead>
<tr>
<th>Acamprosate</th>
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<tr>
<td><strong>Brand Name</strong></td>
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<tr>
<td><strong>Formulation</strong></td>
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<tr>
<td><strong>Dosage</strong></td>
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Acamprosate works by reducing alcohol cravings, which in turn helps people drink less or abstain from alcohol (National Library of Medicine [NLM], 2019a; SAMHSA & National Institute on Alcohol Abuse and Alcoholism [NIAAA], 2015). The exact mechanism of action is not fully understood, but it is hypothesized that acamprosate’s interaction with the glutamatergic neurotransmitter system reduces protracted withdrawal symptoms such as sleep and mood disturbances, which lessens the chance of relapse.

Unlike other AUD medications, acamprosate is not metabolized in the liver, meaning there is no risk of hepatotoxicity and people with liver problems can use the drug. Further, acamprosate does not usually produce severe adverse drug reactions, nor does it come with an FDA boxed warning, which is the agency’s most serious alert used to highlight dangerous and life-threatening risks. As a result, it can be ideal for patients who are currently taking other medications or using illicit substances. This is important for patients currently using opioids (whether for medical or illicit purposes).

Because acamprosate does not interact with alcohol, it can be used by both people who want to reduce the amount they drink and also by those who want to abstain. However, because acamprosate is usually taken multiple times a day, there can be poor medication adherence, especially among patients with memory problems.

Safety Information

**Side effects**

Adverse events are generally mild and may include diarrhea, sweating, dry mouth, flatulence, weakness, insomnia, paresthesia, anxiety, nausea, itching, and dizziness. In an analysis of clinical trials involving 3,725 patients, side effect rates did not differ significantly between acamprosate and control groups, with the exception of the rate of diarrhea. During these studies, diarrhea was recorded in 16 percent of the acamprosate group and resulted in treatment discontinuation for 2 percent of patients. Ten percent of patients treated with placebo experienced diarrhea and 0.7 percent discontinued treatment (NLM, 2019a; SAMHSA & NIAAA, 2015).

Although rare, suicidal ideation and attempts have been reported in clinical trials. The causal relationship between suicidality and acamprosate is unestablished, and the differences in occurrence rates between those treated with acamprosate and placebo were insignificant. Nonetheless, families and caregivers should monitor patients for signs of depression or suicidality and report them to the patient’s healthcare provider (NLM, 2019a; SAMHSA & NIAAA, 2015).

**Contraindications**

Because acamprosate is cleared by the kidneys, caution is merited for people with renal impairment (NLM, 2019a). For patients with severe renal impairment (defined as creatinine clearance of ≤ 30 mL/min), the drug is contraindicated. For those with mild renal impairment (defined as creatinine clearance of 30–50
mL/min), an initial dose of one tablet three times per day is advised. Because older adults are known to have diminished kidney function, they should be evaluated and monitored closely. Acamprosate is also contraindicated for people who have an allergic reaction to the medication. Research is not readily available for pregnant women or adolescents, so prescribers should determine whether the benefits outweigh the risks before beginning treatment (NLM, 2019a; SAMHSA & NIAAA, 2015).

See the [acamprosate safety profile](#) for more detailed information.

### Disulfiram

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Antabuse</th>
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<tbody>
<tr>
<td>Formulation</td>
<td>Oral tablets</td>
</tr>
<tr>
<td>Dosage</td>
<td>Available as either 250- or 500-mg tablets</td>
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</table>

Disulfiram works by inhibiting the liver’s ability to metabolize alcohol. This inhibition leads to very unpleasant physical symptoms following alcohol consumption, known as the disulfiram–alcohol reaction. Avoiding this reaction motivates patients to abstain from using alcohol through negative reinforcement (NLM, 2019b; SAMHSA & NIAAA, 2015). The symptoms of the disulfiram–alcohol reaction vary depending on the patient and can include throbbing in the head and neck, difficulty breathing, headache, nausea, vomiting, thirst, chest pain, sweating, palpitations, hyperventilation, weakness, vertigo, hypotension, and tachycardia. More severe effects can include heart failure, seizures, respiratory depression, and death. However, when taken as directed following physician examination and assessment, disulfiram is generally safe for most patients with AUD.

Research supports the use of disulfiram when patients receive high levels of monitoring and supervision to ensure adherence. Thus, the quality of the monitoring can directly affect treatment outcomes (Center for Substance Abuse Treatment [CSAT], 2009; Martin et al., 2004; Martin et al., 2005; Schuckit, 2006).

Disulfiram is ideal for patients seeking complete abstinence.

### Safety Information

**Side effects**

Disulfiram treatment has been associated with numerous adverse events, including optic neuritis, peripheral neuritis, polyneuritis, peripheral neuropathy, and psychosis. Multiple forms of hepatitis have also been reported, along with hepatic failure that necessitated liver transplant or resulted in death, so prescribers should exercise caution and closely monitor patients with preexisting liver conditions. However, many side effects are often mild, rare, and short-lived. These include slight drowsiness, headache, and acne. Skin eruptions, if they occur, can be managed by concomitant administration of an antihistaminic drug. Side effect severity can vary considerably from person to person, so treatment initiation, maintenance, and possible discontinuation should be tailored to the individual needs and characteristics of each patient (NLM, 2019b; SAMHSA & NIAAA, 2015).
Contraindications
Do not prescribe disulfiram to patients who are using or have recently used metronidazole, paraldehyde, or alcohol (including alcohol-containing products such as cough syrups). Disulfiram is contraindicated for patients with severe myocardial disease, coronary occlusion, and psychoses. Nursing women should not receive disulfiram, nor should anyone with a known hypersensitivity to disulfiram or other thiuram derivatives used in pesticides and rubber hardening.

Although not fully contraindicated, caution is merited when considering disulfiram for older adults, pregnant women, or patients under 18. For older adults, who often have diminished kidney and liver function, lower dosages are generally recommended.

Use extreme caution when prescribing disulfiram to patients with diabetes mellitus, hypothyroidism, epilepsy, cerebral damage, chronic and acute nephritis, and hepatic cirrhosis or insufficiency (NLM, 2019b; SAMHSA & NIAAA, 2015).

See the disulfiram safety profile for more detailed information.

Alcohol use during treatment
Some individuals may continue to use alcohol while they are taking disulfiram, stopping and starting the medication in an attempt to avoid the disulfiram–alcohol reaction. Relapse is common among people with AUD. These behaviors should be anticipated by providers. For the patient’s safety, the patient and family should be frequently and explicitly reminded about the dangers of consuming alcohol while taking disulfiram. The FDA product label for disulfiram contains a boxed warning stating that disulfiram should never be administered to an intoxicated person or without fully informed consent of the patient. A minimum abstinence period of 12 hours is needed before disulfiram administration. Patients should also be aware that disulfiram reacts with alcohol used in foods, medications, tonics, or other sources. Even small amounts of alcohol can trigger physical symptoms, and disulfiram’s effects can last up to 14 days after the medication is last used. It is imperative that prescribers relay this information because common items such as salad dressings, perfume, and hand sanitizer may precipitate a mild negative reaction as well. While disulfiram’s effects can be mild for some, they can be severe for others.

<table>
<thead>
<tr>
<th>Oral Naltrexone</th>
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<tbody>
<tr>
<td><strong>Brand Name</strong></td>
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<tr>
<td><strong>Formulation</strong></td>
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<tr>
<td>** Dosage**</td>
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Naltrexone is an opioid antagonist, meaning it binds to the body’s opioid receptors and blocks the physical and euphoric effects of opioids (NLM, 2017; SAMHSA & NIAAA, 2015). When taking naltrexone, patients experience a reduction in craving for opioids and are unable to experience the pleasurable effects associated with opioid use. Research has shown that alcohol’s effects are at least partly mediated by the body’s opioid receptor system. Thus, by diminishing opioid activity, naltrexone also lessens the gratifying effects of alcohol, which leads to craving reduction and may also lessen the quantity of alcohol consumed (SAMHSA & NIAAA, 2015).
Like acamprosate, oral naltrexone is suited for people who want to reduce their cravings. Aside from opioids, naltrexone does not interact adversely with other medications or substances and, therefore, can be prescribed for people taking other medications or illicit drugs. Further, it can be used for people who are trying either to achieve total abstinence or to reduce their drinking levels. Like acamprosate, oral naltrexone can be used even if patients relapse to alcohol use, as there are no adverse reactions when the substances are mixed.

Because naltrexone is approved for people who have either AUD or opioid use disorder (OUD), it may be an ideal option for people who have both, although XR-NTX is generally recommended over oral naltrexone for treating the latter. Naltrexone is an opioid antagonist, so it is important to ensure that patients are not also using opioids prior to administering naltrexone. Urine screens and the naloxone challenge test are two useful methods to determine this. The latter involves administering naloxone to patients and checking to see if there are any signs of opioid withdrawal, in which case naltrexone would be contraindicated.

**Safety Information**

**Side effects**

Naltrexone is generally safe and well tolerated. Extensive clinical studies that evaluated naltrexone hydrochloride in detoxified, formerly opioid-dependent individuals did not identify any single, serious untoward risk caused by the medication. In other research involving people with AUD, most events reported were rare and/or mild. These included headache (7%), nausea (10%), dizziness (4%), fatigue (4%), vomiting (3%), and somnolence (2%). Other side effects (also rare and/or mild) included diarrhea, stomach pain, joint and muscle pain, rash, blood pressure changes, and sleeping difficulty. There have been instances when people taking naltrexone experienced harm to the kidneys and liver, so caution is needed for patients with renal or hepatic complications. Clinical trial data have also shown incidences of depression and suicidal behavior, although the rates did not differ significantly between the medication and control groups and no causal relationship with naltrexone was suspected. Nonetheless, prescribers should monitor for signs of depression and suicidal ideation while also notifying family members and friends about these potential symptoms and the need to report them if noticed (NLM, 2017; SAMHSA & NIAAA, 2015).

**Contraindications**

Oral naltrexone should not be prescribed to patients currently using opioids. It should also not be used for patients in acute opioid withdrawal or for patients who have recently used opioids. In general, a period of 7–14 days of opioid abstinence is recommended prior to treatment initiation. Useful methods for determining opioid use include urine screens and the naloxone challenge. The latter involves administering naloxone to patients and observing for any signs of opioid withdrawal (NLM, 2017; SAMHSA & NIAAA, 2015).

**RESOURCE ALERT**

**Naltrexone for People With OUD**

When considering naltrexone treatment, providers should encourage their patients to disclose opioid use and should also conduct physical tests to reveal opioid presence in the body. For more information on naltrexone for people with OUD, refer to the following sources from SAMHSA and the American Society of Addiction Medicine (ASAM):

- [TIP 63: Medications for Opioid Use Disorder](#)
- [The ASAM National Practice Guideline for the Treatment of Opioid Use Disorder—2020 Focused Update](#)
Research is not readily available on naltrexone for pregnant women, women who are nursing, or pediatric populations, so treatment benefits must be weighed against the risks. For older adults, available research suggests naltrexone is safe and tolerable, but large-scale studies have not been conducted with this population (SAMHSA, 2020c).

Caution is merited for patients who are likely to relapse to opioid use. This is especially important because some people may attempt to override the opioid blockade, which can lead to overdose and death. Further, patients who have been opioid abstinent may not realize that they have a reduced tolerance and are at higher risk of overdose. Patients with a known sensitivity to naltrexone or any of the components found in the tablet should not receive it.

See the oral naltrexone safety profile for more detailed information.

Extended-Release Injectable Naltrexone (XR-NTX)

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Vivitrol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formulation</td>
<td>Injection</td>
</tr>
<tr>
<td>Dosage</td>
<td>Injection of 380-mg microspheres embedded in biodegradable material received every 4 weeks via intramuscular (IM) injection</td>
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</tbody>
</table>

XR-NTX contains the same active ingredient as oral naltrexone and has the same mechanism of action as its oral counterpart. That is, it blocks the euphoric effects of opioids, which can also lessen the pleasurable effects of alcohol and reduce cravings. The difference lies in the rate at which the medication enters the body and the way it is supplied (NLM, 2020; SAMHSA & NIAAA, 2015).

XR-NTX is not immediately absorbed but is instead metabolized over an extended period. The medication is administered via IM injection in the gluteal region. Two needle lengths are available: 1.5 inches (for very lean patients) and 2 inches (for patients with ample subcutaneous tissue covering the gluteal region). Either needle can be used for average-sized patients.

Ideal candidates for XR-NTX are people whose goals may be either reduced drinking or total abstinence and who seek a medication that can reduce cravings. Like oral naltrexone, XR-NTX is FDA approved for treating OUD as well, although research has shown that its treatment outcomes are far superior to oral naltrexone, which makes it the preferred antagonist for treating OUD (SAMHSA, 2020b).

The advantage of XR-NTX over the other medications is patient adherence. This is useful not only for people who may purposely not take their medication, but also for individuals with cognitive impairment (who may simply forget). XR-NTX may be the optimal solution for patients who do not have anyone to monitor their medication adherence.

Naltrexone is an opioid antagonist, so it is important to ensure that patients are not also using opioids prior to administering naltrexone. Urine screens and the naloxone challenge test are two useful methods to determine this. The latter involves administering naloxone to patients and checking to see if there are any signs of opioid withdrawal, in which case naltrexone would be contraindicated.
Safety Information

Side effects
XR-NTX has the same side effects and precautions as its oral counterpart. Additional adverse events can result from injection site complications. These include intense pain, hardness, swelling, lumps, blistering, sores, scabs, open wounds, and tissue death (necrosis). Sometimes reactions are serious enough to require surgery. Prescribers should also use caution when administering the medication to people with thrombocytopenia as well as hemophilia or other types of coagulation disorders (Alkermes, n.d.; NLM, 2020).

Contraindications
XR-NTX has the same contraindications as its oral counterpart and should generally be given to patients who have been abstinent from opioids for 7–14 days. For some individuals, however, earlier induction procedures may prove beneficial (SAMHSA, 2020b).

See the [XR-NTX safety profile](#) for more detailed information.

Pain Treatment for Patients Taking Naltrexone

Pain management can be complicated in naltrexone-maintained patients. For mild pain, nonopioid analgesics such as acetaminophen, aspirin, and ibuprofen may be used. Other options include regional anesthesia, conscious sedation with benzodiazepines or ketamine, and general anesthesia without opioids.

For some patients, however, these choices may not be suitable due to associated adverse events and/or a need for higher potency analgesics (i.e., opioids). If the need for opioids is known in advance (e.g., a planned surgery), patients taking oral naltrexone should discontinue the medication at least 3 days prior to opioid treatment. Patients taking XR-NTX should stop 30 days prior to opioid administration and take oral naltrexone until about 3 days before the procedure. In general, patients can resume naltrexone treatment (with either formulation) 3–7 days after they have discontinued using their prescribed opioids (ASAM, 2020; NLM, 2017, 2020; SAMHSA, 2020b).

Sometimes, emergency opioid pain treatment will be needed. Current guidelines recommend using higher potency opioids to overcome the blockade, which requires close patient monitoring in an emergency department or hospital setting that has personnel and equipment capable of carrying out cardiopulmonary resuscitation (ASAM, 2020; NLM, 2017, 2020; SAMHSA, 2020b).

Patient Management

AUD, like most diseases, requires a multifaceted approach to ensure optimal treatment outcomes. With AUD pharmacotherapy, the first step is evaluating the patient to determine which medication will have the greatest benefit. During patient evaluation, careful consideration of preexisting conditions and patient preferences are necessary first steps. The chart below provides an overview of common conditions that are present in people with AUD, along with medication considerations for each. It summarizes much of the safety information found in the previous sections.
### Pretreatment Indicators and Medications

<table>
<thead>
<tr>
<th>Pretreatment Indicators</th>
<th>Medications</th>
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<tbody>
<tr>
<td></td>
<td>Acamprosate</td>
</tr>
<tr>
<td>Liver disease</td>
<td>A</td>
</tr>
<tr>
<td>Kidney failure</td>
<td>X</td>
</tr>
<tr>
<td>Chronic pain</td>
<td>A</td>
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<tr>
<td>Severe myocardial disease</td>
<td>A</td>
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<tr>
<td>Diabetes mellitus</td>
<td>A</td>
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<tr>
<td>Current opioid use</td>
<td>A</td>
</tr>
<tr>
<td>Psychosis</td>
<td>A</td>
</tr>
<tr>
<td>Obesity that precludes IM injection</td>
<td>A</td>
</tr>
<tr>
<td>OUD in remission</td>
<td>A</td>
</tr>
</tbody>
</table>

*A = Appropriate for use  C = Use with caution  X = Contraindicated

*Naltrexone is approved to treat both AUD and OUD and may be especially beneficial for some patients with both disorders. However, for OUD, XR-NTX is usually recommended over oral naltrexone due to low adherence rates in the latter.

### Common Laboratory Tests

Various laboratory tests are needed before a prescription can be written for AUD medications (CSAT, 2009):

- Urine toxicology
- Liver function tests
- Complete blood count
- Test for vitamin deficiencies
- Renal function tests
- Pregnancy test (for women of childbearing age)

### Psychotherapy and Mutual Help

For most patients with AUD, evidence-based psychotherapeutic interventions play a vital role. Some patients may prefer to see a psychologist, psychiatrist, or professional counselor. Others may want to participate in mutual-help groups. Discussions with patients are needed to see which approach best fits their preferences and circumstances. Various mobile applications (like Sober Grid, whose development was funded by the National Institutes of Health and the National Science Foundation), are also available to help people find support.
Promoting Treatment Adherence
For medications that require multiple doses throughout the day, providers can suggest that patients wear reminder bracelets that will help them stay on track; set alarms on their watches, phones, or other devices; and/or engage in daily rituals that will make the treatment easier to remember. To help patients stay motivated, inquire if they have family members, friends, or other people in their social networks who can help them maintain their progress. In particular, ask if they know people they can rely on to observe their daily dosing regimen. These individuals need not be in the same location as the patient and can observe via their computers or mobile devices.

Follow-Up
Important points to consider for any follow-up visit include:

- Whether the patient is making progress.
- If the medication is causing any adverse reactions not previously seen.
- **If there is any change in the patient’s physical or mental health.**
- If the patient is taking any new medications since the last visit.
- Whether the patient has relapsed.

Any of these factors, especially relapse, may be cause for treatment modification.

Modifying Treatment in Event of Relapse
If patients relapse to alcohol use, there are several strategies to get them back on track (CSAT, 2009). Such strategies should be extensively discussed with the patient so that their consent and buy-in are obtained:

- Change medication
- Increase the dosage
- Explore ways to increase patient monitoring and motivation
- Change the type of psychosocial treatment or increase the amount of time patients spend in treatment
- Talk with patients about the triggers that led to the relapse and see if there are ways for them to avoid being in situations where those triggers are present

Discontinuing Treatment
Some patients may only want to take AUD medication during a difficult time in their lives to help them avoid drinking, while others may benefit from taking it over an extended period or indefinitely. Changes in the patient’s health status may also require medication discontinuation. Additionally, patients may begin to experience medication side effects that were not present during the initial treatment phase (CSAT, 2009).

Ideally, patients will discontinue medication when they feel they can achieve their goals of abstinence or reduced alcohol intake. None of the AUD medications have significant withdrawal symptoms reported and thus do not require tapering. However, patients should be reminded that the effects of their medication can last long after discontinuation. This is especially important for patients using disulfiram and XR-NTX, whose adverse events and drug interactions can continue for a few weeks (CSAT, 2009).
Resources

- **Substance Abuse and Mental Health Services Administration (SAMHSA)**
  - FindTreatment.gov
  - *Medication for the Treatment of Alcohol Use Disorder: A Brief Guide*
  - SAMHSA Behavioral Health Treatment Services Locator
  - TIP 42, *Substance Use Disorder Treatment for Persons With Co-Occurring Disorders*
  - TIP 49, *Incorporating Alcohol Pharmacotherapies Into Medical Practice*
- **Alcoholics Anonymous (AA)**
- **American Psychiatric Association (APA)**
  - *Practice Guideline for the Pharmacological Treatment of Patients With Alcohol Use Disorder*
- **National Institute on Alcohol Abuse and Alcoholism (NIAAA)**
  - NIAAA Alcohol Treatment Navigator
  - *Treatment for Alcohol Problems: Finding and Getting Help*
- **National Institute on Drug Abuse (NIDA)**
  - Alcohol Use Disorders Identification Test (AUDIT)
- **Smart Recovery**
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Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality. (2020a). Results from the 2019 National Survey on Drug Use and Health: Detailed tables (Tables 2.1A and 5.1A). www.samhsa.gov/data/


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