# Pharmacotherapy for Alcohol Use Disorder

| | Naltrexone Oral | Naltrexone Injectable | Acamprosate | Disulfiram | Topiramate[1] | Gabapentin[1] |
|---|---|---|---|---|---|---|
| **Indications** | **AUD (DSM diagnosis) with:**<br>– Pretreatment abstinence not required but may improve response<br>– Initial engagement in addiction-focused medical management and/or other recommended psychosocial intervention | **AUD (DSM diagnosis) with:**<br>– Pretreatment abstinence not required but may improve response<br>– Willingness to receive monthly injections<br>– Difficulty adhering to an oral regimen<br>– Initial engagement in addiction-focused medical management and/or other recommended psychosocial intervention | **AUD (DSM diagnosis) with:**<br>– Abstinence at treatment initiation<br>– Initial engagement in addiction-focused medical management and/or other recommended psychosocial intervention | **AUD (DSM diagnosis) with:**<br>– Abstinence > 12 hours and BAL = 0<br>– Combined cocaine dependence<br>– Previous response to disulfiram<br>– Capacity to appreciate risks and benefits and to consent to treatment<br>– Initial engagement in addiction-focused medical management and/or other recommended psychosocial intervention<br>– **Note:** more effective with monitored administration (i.e. in clinic, with spouse, with probation officer) | **AUD (DSM diagnosis) [off label] with:**<br>– Pretreatment abstinence not required but may improve response<br>– Initial engagement in addiction-focused medical management and/or other recommended psychosocial intervention | **AUD (DSM diagnosis) [off label] with:**<br>– Pretreatment abstinence not required but may improve response<br>– Initial engagement in addiction-focused medical management and/or other recommended psychosocial intervention |
| **Contraindications** | – Receiving opioid agonists<br>– Physiologic opioid dependence with use within past 7 days<br>– Acute opioid withdrawal<br>– Failed naloxone/ naltrexone challenge test<br>– Positive urine opioid screen<br>– Acute hepatitis or liver failure<br>– Hypersensitivity | – Receiving opioid agonists<br>– Physiologic opioid dependence with use within past 7 days<br>– Acute opioid withdrawal<br>– Failed naloxone/ naltrexone challenge test<br>– Positive urine opioid screen<br>– Acute hepatitis or liver failure<br>– Hypersensitivity<br>– Inadequate muscle or body habitus too large for supplied injection needle | – Hypersensitivity<br>– Severe renal insufficiency (CrCl ≤ 30 mL/min) | – Severe cardiovascular, respiratory, or renal disease<br>– Severe hepatic dysfunction (i.e. transaminase level > 3 times upper limit of normal or abnormal bilirubin)<br>– Severe psychiatric disorders, especially psychotic and cognitive disorders and suicidal ideation<br>– Poor impulse control<br>– Metronidazole or ketoconazole therapy, which already induce a similar reaction to alcohol<br>– Hypersensitivity | – No contraindications in manufacturer's labeling | – Hypersensitivity<br>– History of misuse |

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| **Warnings/ Precautions** | – Active liver disease<br>– Severe renal failure<br>– Breastfeeding—not advised, proven teratogenicity in animal studies<br>– Acute/chronic pain<br>– History of severe depression, acute psychiatric illness<br>– Pregnancy category C | – Active liver disease<br>– Uncertain effects (no data) in moderate to severe renal insufficiency<br>– Injection site reactions<br>– Use intramuscular injections with caution in patients with thrombocytopenia or coagulation disorders<br>– Breastfeeding—not advised, proven teratogenicity in animal studies<br>– Acute/chronic pain<br>– History of severe depression, acute psychiatric illness<br>– Pregnancy category C | – Monitor for emergence of depression or suicidality<br>– Reduce dose in patients with renal insufficiency, including the elderly<br>– Pregnancy category C | – Alcohol-disulfiram reaction; patients must be vigilant to avoid alcohol in all forms, including mouthwash, over-the-counter medications, etc.<br>– Pregnancy category C | – Do not abruptly discontinue therapy; taper dosage gradually<br>– Cognitive dysfunction, psychiatric disturbances, and sedation may occur with use<br>– Increased risk of suicidal ideation with antiepileptic agents, including topiramate<br>– Pregnancy category C | – Do not abruptly discontinue therapy; taper dosage gradually<br>– May cause CNS depression, including somnolence/dizziness<br>– Increased risk of suicidal ideation with antiepileptic agents, including topiramate<br>– Pregnancy category C |
| **Baseline Evaluation** | – Liver transaminase levels<br>– Bilirubin within normal limits<br>– Urine beta-HCG for females<br>– Toxicology screen | – Liver transaminase levels<br>– Bilirubin within normal limits<br>– CrCl (estimated or measured) ≥ 50 mL/min<br>– Ensure patient has adequate muscle for injection<br>– Urine beta-HCG for females<br>– Toxicology screen | – CrCl (estimated or measured)<br>– Urine beta-HCG for females | – Liver transaminase levels<br>– Physical assessment<br>– Psychiatric assessment<br>– Electrocardiogram if indicated by history of cardiac disease<br>– Verify abstinence with breath or BAL<br>– Urine beta-HCG for females | – Assess renal function<br>– Urine beta-HCG for females | – Assess renal function<br>– Urine beta-HCG for females |
| **Dosage and Administration** | – 50-100 mg orally 1 time daily | – 380 mg 1 time monthly by deep intramuscular injection | – 666 mg orally 3 times daily, preferably with meals | – 250 mg orally 1 time daily (range, 125-500 mg daily) | – Titrate up gradually over several weeks to minimize side effects<br>– Initiate at 50 mg/day; increase to a maximum dose of 100 mg 2 times daily | – Titrate up gradually over several weeks to minimize side effects<br>– Initiate at 300 mg on day 1 and increase by 300 mg daily as tolerated to target of 1800 mg daily, administered in 3 divided doses |
| **Alternative Dosing Schedules** | – 25 mg 1 or 2 time(s) daily with meals to reduce nausea, especially during the first week<br>– 100 mg on Monday and Wednesday and 150 mg on Friday | – Geriatric patients with CrCl < 70 mL/min/1.73m$^2$: give initial dose of 25 mg/day followed by incremental increases of 25 mg at weekly intervals until an effective dose is reached | – NA | – Reduce dose to 125 mg to reduce side effects<br>– For monitored administration, consider giving 500 mg on Monday, Wednesday, and Friday | | – NA |

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| **Dosing in Special Populations** | – **Hepatic or renal insufficiency:** use caution | – **Mild renal insufficiency (CrCl 50-80 mL/min):** no dosage adjustment necessary<br>– Uncertain effects (no data) in moderate to severe renal insufficiency | – **Moderate renal insufficiency (CrCl 30-50 mL/min):** 333 mg 3 times daily<br>– Do not administer to patients with severe renal insufficiency (CrCl ≤ 30 mL/min) | – NA | – **CrCl < 70 mL/min/1.73m$^2$:** administer 50% dose and titrate more slowly<br>– **CrCl < 70 mL/min/1.73m$^2$:** administer 50% dose and titrate more slowly | – Dosage must be adjusted for renal function, consider target dose < 1800 mg daily when CrCl < 60 mL/min |
| **Adverse Effects** | – **Common:** Nausea<br>– **Other:** Headache, dizziness, nervousness, fatigue, insomnia, vomiting, anxiety, somnolence | – **Major:** Eosinophilic pneumonia, depression, suicidality<br>– **Common:** Injection-site reactions, injection-site tenderness, injection-site induration, nausea, headache, asthenia | – **Major:** Suicidality 2.4% (vs. 0.8% on placebo during first year in clinical trials)<br>– **Common:** Diarrhea (16%)<br>– **Other:** Anxiety, asthenia, depression, insomnia | – **Major:** Hepatoxicity, peripheral neuropathy, psychosis, delirium, severe disulfiram-ethanol reaction<br>– **Common:** Somnolence, metallic taste, headache | – **CNS:** Paresthesia, nervousness, fatigue, ataxia, drowsiness, lack of concentration, memory impairment, confusion<br>– **Gastrointestinal:** Abdominal pain, anorexia | – **CNS:** Dizziness, drowsiness, ataxia, fatigue<br>– **Gastrointestinal:** diarrhea, nausea/vomiting, abdominal pain |
| **Drug Interactions** | – Opioid-containing medication, including over-the-counter preparations<br>– Thioridazine (increased lethargy and somnolence) | – Opioid-containing medication, including over-the-counter preparations<br>– Thioridazine (increased lethargy and somnolence) | – **Naltrexone:** 33% increase in Cmax of acamprosate (no dosage adjustment is recommended)<br>– **Antidepressants:** Weight gain and weight loss more common than with either medication alone | – Alcohol-containing medication, including over-the-counter preparations<br>– Drug-drug interactions may occur with phenytoin, warfarin, isoniazid, rifampin, diazepam, chlordiazepoxide, imipramine, desipramine, and oral hypoglycemic agents | – Use extreme caution if used concurrently with alcohol or other CNS depressants<br>– Topiramate may decrease the serum concentrations of contraceptives and decrease their effectiveness | – Use extreme caution if used concurrently with alcohol or other CNS depressants<br>– Antacids may decrease levels of gabapentin |
| **Monitoring** | – Repeat liver transaminase levels at 6 and 12 months and then every 12 months thereafter<br>– Discontinue medication and consider alternatives if no detectable benefit after an adequate trial (50 mg daily for 3 months) | – Repeat liver transaminase levels at 6 and 12 months and then every 12 months thereafter<br>– Discontinue medication and consider alternatives if no detectable benefit after an adequate trial | – Monitor serum creatinine/CrCl, particularly in the elderly and in patients with renal insufficiency<br>– Maintain therapy if relapse occurs | – Repeat liver transaminase levels within the first month, then monthly for first 3 months and periodically thereafter as indicated<br>– Consider discontinuation in event of relapse or when patient is not available to be supervised or counseled | – Monitor serum creatinine/CrCl periodically, particularly in patients with renal insufficiency and in geriatric patients<br>– Monitor for change in behavior that might indicate suicidal thoughts or depression<br>– Discontinue medication and consider alternatives if no detectable benefit after an adequate trial (300 mg daily for 3 months) | – Monitor serum creatinine/CrCl periodically, particularly in patients with renal insufficiency and in geriatric patients<br>– Monitor for change in behavior that might indicate suicidal thoughts or depression<br>– Gabapentin has the potential for misuse when taken in supratherapeutic doses; monitor quantities prescribed and usage patterns<br>– Discontinue medication and consider alternatives if no detectable benefit from at least 900 mg daily for 2-3 months |

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| **Patient Education** | – Discuss compliance-enhancing methods<br>– Negotiate commitment from patient regarding monitored ingestion<br>– Side effects, if any, tend to occur early in treatment and can typically resolve within 1-2 weeks after dose adjustment<br>– If signs and symptoms of acute hepatitis occur, discontinue naltrexone and contact provider immediately<br>– Very large doses of opioids may overcome the effects of naltrexone and lead to serious injury, coma, or death<br>– Small doses of opioids, such as in analgesic, antidiarrheal, or antitussive drugs may be blocked by naltrexone and fail to produce a therapeutic effect<br>– Patients who have previously used opioids may be more sensitive to toxic effects of opioids after discontinuing naltrexone | – Report any concerning injection site reactions<br>– Report any new or worsening depression or suicidal thoughts<br>– May cause allergic pneumonia; contact provider if patient develops signs and symptoms of pneumonia | – Report any new or worsening depression or suicidal thoughts | – Avoid alcohol in food and beverages, including medications<br>– Avoid disulfiram if alcohol intoxication is present<br>– May cause sedation; use caution operating vehicles and hazardous machinery<br>– Discuss compliance-enhancing methods<br>– Family members should not administer disulfiram without informing patient<br>– Provide patients with wallet cards that indicate the use of disulfiram | – Administer without regard to meals<br>– It is not recommended to crush, break, or chew immediate-release tablets due to bitter taste<br>– Caution patients about performing tasks requiring mental alertness | – Take first dose on first day at bedtime to minimize somnolence and dizziness<br>– Caution patients about performing tasks requiring mental alertness |

[1] Not FDA-labeled for treatment of AUD

**Abbreviations:** AUD: alcohol use disorder; BAL: blood alcohol level; Cmax: maximum concentration; CNS: central nervous system; CrCl: creatinine clearance; DSM: Diagnostic and Statistical Manual of Mental Disorders; HCG: human chorionic gonadotropin; m: meter(s); mg: milligram(s); min: minute(s); mL: milliliter(s)

Adapted from Department of Veteran Affairs. The Management of Substance Use Disorders Work Group. (December 2015). *VA/DoD Clinical Practice Guideline for the Management of Substance Use Disorders*. Version 3.0-2015.