Pharmacotherapy for Alcohol Use Disorder

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

Pharmacotherapy for Alcohol Use Disorder *(continued)*

	Naltrexone Oral	Naltrexone Injectable	Acamprosate	Disulfiram	Topiramate[1]	Gabapentin[1]
Warnings/ Precautions	– Active liver disease – Severe renal failure – Breastfeeding—not advised, proven teratogenicity in animal studies – Acute/chronic pain – History of severe depression, acute psychiatric illness – Pregnancy category C	– Active liver disease – Uncertain effects (no data) in moderate to severe renal insufficiency – Injection site reactions – Use intramuscular injections with caution in patients with thrombocytopenia or coagulation disorders – Breastfeeding—not advised, proven teratogenicity in animal studies – Acute/chronic pain – History of severe depression, acute psychiatric illness – Pregnancy category C	– Monitor for emergence of depression or suicidality – Reduce dose in patients with renal insufficiency, including the elderly – Pregnancy category C	– Alcohol-disulfiram reaction; patients must be vigilant to avoid alcohol in all forms, including mouthwash, over-the-counter medications, etc. – Pregnancy category C	– Do not abruptly discontinue therapy; taper dosage gradually – Cognitive dysfunction, psychiatric disturbances, and sedation may occur with use – Increased risk of suicidal ideation with antiepileptic agents, including topiramate – Pregnancy category C	– Do not abruptly discontinue therapy; taper dosage gradually – May cause CNS depression, including somnolence/dizziness – Increased risk of suicidal ideation with antiepileptic agents, including topiramate – Pregnancy category C
Baseline Evaluation	– Liver transaminase levels – Bilirubin within normal limits – Urine beta-HCG for females – Toxicology screen	– Liver transaminase levels – Bilirubin within normal limits – CrCl (estimated or measured) ≥ 50 mL/min – Ensure patient has adequate muscle for injection – Urine beta-HCG for females – Toxicology screen	– CrCl (estimated or measured) – Urine beta-HCG for females	– Liver transaminase levels – Physical assessment – Psychiatric assessment – Electrocardiogram if indicated by history of cardiac disease – Verify abstinence with breath or BAL – Urine beta-HCG for females	– Assess renal function – Urine beta-HCG for females	– Assess renal function – 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 – 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 – 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 – 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 – 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 – Uncertain effects (no data) in moderate to severe renal insufficiency	– **Moderate renal insufficiency (CrCl 30-50 mL/min):** 333 mg 3 times daily – 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 – **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 – **Other:** Headache, dizziness, nervousness, fatigue, insomnia, vomiting, anxiety, somnolence	– **Major:** Eosinophilic pneumonia, depression, suicidality – **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) – **Common:** Diarrhea (16%) – **Other:** Anxiety, asthenia, depression, insomnia	– **Major:** Hepatoxicity, peripheral neuropathy, psychosis, delirium, severe disulfiram-ethanol reaction – **Common:** Somnolence, metallic taste, headache	– **CNS:** Paresthesia, nervousness, fatigue, ataxia, drowsiness, lack of concentration, memory impairment, confusion – **Gastrointestinal:** Abdominal pain, anorexia	– **CNS:** Dizziness, drowsiness, ataxia, fatigue – **Gastrointestinal:** diarrhea, nausea/vomiting, abdominal pain
Drug Interactions	– Opioid-containing medication, including over-the-counter preparations – Thioridazine (increased lethargy and somnolence)	– Opioid-containing medication, including over-the-counter preparations – Thioridazine (increased lethargy and somnolence)	– **Naltrexone:** 33% increase in Cmax of acamprosate (no dosage adjustment is recommended) – **Antidepressants:** Weight gain and weight loss more common than with either medication alone	– Alcohol-containing medication, including over-the-counter preparations – 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 – Topiramate may decrease the serum concentrations of contraceptives and decrease their effectiveness	– Use extreme caution if used concurrently with alcohol or other CNS depressants – Antacids may decrease levels of gabapentin
Monitoring	– Repeat liver transaminase levels at 6 and 12 months and then every 12 months thereafter – 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 – 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 – Maintain therapy if relapse occurs	– Repeat liver transaminase levels within the first month, then monthly for first 3 months and periodically thereafter as indicated – 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 – Monitor for change in behavior that might indicate suicidal thoughts or depression – 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 – Monitor for change in behavior that might indicate suicidal thoughts or depression – Gabapentin has the potential for misuse when taken in supratherapeutic doses; monitor quantities prescribed and usage patterns – Discontinue medication and consider alternatives if no detectable benefit from at least 900 mg daily for 2-3 months

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

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