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## Pharmacotherapy for alcohol use disorder

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**INTRODUCTION** — The World Health Organization estimated that more than 75 million people had alcohol abuse or dependence worldwide over a 12 month period [1]. Nearly two million deaths each year have been attributed to the disorders. The prevalence of alcohol use disorders in primary care ranges from 20 to 36 percent, although the conditions are frequently untreated [2,3].

Psychosocial interventions are effective in the treatment of alcohol abuse and dependence; however, as many as 70 percent of individuals relapse after psychosocial treatment alone [4-7]. Several medications can be used to treat alcohol use disorder, leading to reduced heavy drinking and increased days of abstinence [8]. There is little evidence on the effectiveness of medication in the treatment of nondependent alcohol abuse.

The psychiatric diagnoses, alcohol abuse and alcohol dependence, in DSM-IV-TR were replaced by one diagnosis, alcohol use disorder, in DSM-5 [9]. Although the crosswalk between DSM-IV and DSM-5 disorders is imprecise, alcohol dependence is approximately comparable to alcohol use disorder, moderate to severe subtype, while alcohol abuse is similar to the mild subtype.

This topic focuses on medication in the treatment of alcohol use disorder. The epidemiology, pathogenesis, clinical manifestations, assessment, and diagnosis of alcohol use disorder, as well as psychosocial treatments for the disorder, are discussed separately. (See "Risky drinking and alcohol use disorder: Epidemiology, pathogenesis, clinical manifestations, course, assessment, and diagnosis" and "Psychosocial treatment of alcohol use disorder" and "Screening for unhealthy use of alcohol and other drugs in primary care" and "Brief intervention for unhealthy alcohol and other drug use".)

**NEUROBIOLOGY** — Pharmacologic treatment of alcohol use disorder has mostly focused on altering the reinforcing effects of alcohol use. Medication development has focused on several neurotransmitter systems that interact with the corticomesolimbic dopamine (CMDA) pathway, which can mediate reinforcement. Many available or promising compounds appear to act by modulating the function of opioids, glutamate (with or without gamma aminobutyric acid, GABA), and serotonin (5-HT).

Some alcohol-dependent individuals possess a biological predisposition to the disease. These biologically vulnerable alcoholics may benefit from specific adjunctive medications addressing the underlying abnormalities.

## TREATMENT PRINCIPLES AND OVERVIEW

**Indications** — Nearly all clinical trials finding medications efficacious for alcohol use disorders studied recently abstinent patients with a DSM-IV-TR diagnosis of alcohol dependence. Applying these findings to patients diagnosed under DSM-V is imprecise, but the most closely comparable group of patients are those with alcohol use disorder, moderate to severe subtype (ie, patients with four or more symptoms within a 12-month period) [9]. DSM-V criteria for the diagnosis of alcohol use disorder are described separately. (See "[Risky drinking and alcohol use disorder: Epidemiology, pathogenesis, clinical manifestations, course, assessment, and diagnosis](#)".)

Pharmacotherapy should be used in patients with alcohol use disorder, moderate to severe subtype, who:

- Have current, heavy use and ongoing risk for consequences from use
- Are motivated to reduce alcohol intake
- Prefer medication along with or instead of a psychosocial intervention
- Do not have medical contraindications to the individual drug

Most data on the efficacy of pharmacotherapy are not generalizable to patients with the mild subtype of alcohol use disorder. Patients with a mild subtype alcohol use disorder who are currently drinking heavily and risk serious consequences can be considered for these treatments on a case-by-case basis.

**Goals** — The traditional goal of treatment for alcohol use disorder is abstinence, which remains a primary treatment focus. In addition, reduction of heavy drinking has become accepted as an alternative treatment goal. The frequency of heavy drinking (defined as more than five drinks per day for men and four for women) shows the highest correlation with negative life consequences such as impaired driving, interpersonal problems, and injuries [10]. Reduction of heavy drinking may be a more acceptable goal for some patients who lack readiness to quit drinking [11].

**Initiation and duration** — Pharmacologic treatment for alcohol use disorder is often initiated during hospitalization for alcohol intoxication or withdrawal. (See "[Medically supervised alcohol withdrawal in the ambulatory setting](#)" and "[Management of moderate and severe alcohol withdrawal syndromes](#)".)

Naltrexone can be initiated while the individual is still drinking. This permits treatment for alcohol use disorder to be provided in community-based practice at the point of maximum crisis without the need for enforced abstinence or detoxification [12]. Disulfiram, which by intent leads to adverse effects when combined with alcohol intake, should only be used by abstinent patients in the context of treatment intended to maintain abstinence. Research indicates that acamprosate should be used once abstinence is achieved.

After initiating medication treatment, follow-up visits should be sufficiently frequent to provide the patient with encouragement and support, to engage family members if helpful, and to monitor the patients for treatment response, side effects, medication adherence, and early signs of relapse, which can lead to serious complications [13].

The optimal duration of pharmacotherapy is not known. Most trials studied the effect of treatment over two to six months. Experts recommend at least six months of medication with an additional six months of follow-up. The efficacy of medication treatment wanes once medications are discontinued. Of the medications described below, only topiramate requires a taper to discontinue, over a two-week period.

**FIRST-LINE MEDICATIONS** — Naltrexone cannot be given to patients taking opioids. If opioids are required to treat pain, naltrexone should be discontinued. Naltrexone is contraindicated in acute hepatitis or liver failure.

**Oral naltrexone** — Naltrexone exerts its principal pharmacological effects through blockade of the mu-opioid receptor. Endogenous opioids are involved in modulating the expression of alcohol's reinforcing effects [14,15]. Mice that lack the mu-opioid receptor do not self-administer alcohol [16]. Naltrexone also modulates the hypothalamic-pituitary-adrenal axis to suppress ethanol consumption [17].

The usual dose of naltrexone is 50 mg/day, but some trials have used up to 100 mg/day [18].

**Efficacy** — Multiple metaanalysis of clinical trials for alcohol dependence found naltrexone to reduce alcohol consumption compared with placebo [19,20]. As an example, a 2010 meta-analysis of 50 randomized trials with 7793 alcohol dependent participants found that naltrexone reduced the risk of heavy drinking to 83 percent of the risk in the placebo group (relative risk [RR] 0.83, 95% CI 0.76-0.90) and decreased drinking days by about 4 percent [20].

Naltrexone may be particularly efficacious in individuals with genetic susceptibility. Preliminary evidence suggests that individuals with the Asp variant of the OPRM1 gene are less likely to experience relapse when receiving naltrexone, but further study is needed to confirm the finding [18,21]. Patients who were heterozygous for the Asp-40 allele were almost six times more likely to have a favorable outcome with naltrexone treatment than those who did not carry this allele.

**Adverse effects** — Common side effects of oral naltrexone are nausea, headache, and dizziness, which subside with continued use. Fivefold elevation in liver enzymes occurred in 11 of 614 patients who received naltrexone in the COMBINE Study. Enzyme levels returned to baseline after discontinuation of medication in the nine patients who had stopped drinking and returned for follow-up [18]. Liver enzymes should be monitored periodically during naltrexone treatment.

**Depot naltrexone** — Depot preparations of naltrexone may improve adherence by reducing the frequency of medication administration from daily to monthly and by achieving a steady therapeutic level of medication, thus avoiding peak effects that can exacerbate adverse events [22]. There are three extended-release, injectable formulations of naltrexone (Vivitrol, Naltrel, and Depotrex). There are no published head-to-head comparisons of their efficacy or bioavailability.

Only Vivitrol has been approved for use in the US, at a dose of 380 mg every four weeks. The injectable suspension should be administered via intramuscular injection to the gluteal area using the provided 1.5 inch 20-gauge needle. The US Food and Drug Administration has warned against other forms of administration including IV or injection subcutaneously or into fatty tissue on the basis of post-marketing reports of serious injection site reactions (See 'Adverse effects' above.).

**Efficacy** — A large randomized trial found subjects receiving Vivitrol 380 mg monthly had a 25 percent greater reduction in the rate of heavy drinking after 24 weeks compared with those receiving placebo (HR 0.75, 95% CI 0.60-0.94) [23]. While subgroup analysis suggested that the treatment may be less effective in women, the proportion of women in this study was relatively small, and these findings may be due to patient characteristics that differed between men and women.

A multi-site randomized trial of the Naltrel formulation did not show a significant difference in the primary outcome, time to first heavy-drinking day, compared with placebo (median of 11 versus 6 days) [24]. However, Naltrel was more efficacious than placebo at increasing the mean number of abstinent days (53 versus 46 days).

**Adverse effects** — Common adverse events observed among subjects receiving Vivitrol included nausea (33 percent), fatigue (20 percent), and decreased appetite (13 percent). Serious adverse events were reported for two trial participants receiving naltrexone who experienced an interstitial pneumonia and an allergic-type eosinophilic pneumonia, both of which resolved with treatment.

In 2008, the Food and Drug Administration (FDA) in the United States (US) reported 196 cases of serious injection site reactions from post-marketing surveillance including induration, cellulitis, hematoma, abscess, and necrosis. The FDA advised that patients be told to report injection-site pain,

swelling, bruising, pruritus, or redness that does not improve within two weeks, and that a surgical consult be considered for worsening reactions [25].

**Acamprosate** — Acamprosate's principal anti-drinking neurochemical effect has been attributed to the modulation of glutamate neurotransmission at metabotropic-5 glutamate receptors [26].

The usual dose for acamprosate is 666 mg three times daily. Lower doses should be considered for some patients, including those with renal impairment, body weight less than 60 kg, or a history of response to a lower dose.

**Efficacy** — Multiple metaanalysis have found acamprosate to reduce alcohol consumption compared with placebo in patients with alcohol dependence [19,27]. As an example, a meta-analysis of 24 randomized trials of 6915 participants compared treatment with acamprosate to placebo or active control [27]. Acamprosate reduced the rate of patients returning to any drinking (relative risk [RR] 0.86, 95% CI 0.81-0.91; NNT = 9) and increased the cumulative abstinence duration by an average of 11 percent. Acamprosate was found not to have a significant effect on heavy drinking.

The evidence on the efficacy of acamprosate has evolved over time and requires further investigation. A 2004 meta-analysis of the 17 European trials found that acamprosate increased six-month abstinence rates compared with placebo (36.1 versus 23.4 percent) [28]. Positive results were primarily seen for maintenance of abstinence rather than reduction of drinking by non-abstinent patients.

Three subsequent trials conducted in the US and Australia found acamprosate did not improve primary outcomes, including percentage of alcohol-free days and time to first heavy drinking [18,29,30]. One of the trials, the COMBINE Study, found acamprosate (either alone or in conjunction with a psychosocial intervention) to be no more effective than placebo, while naltrexone was significantly more effective than placebo, indicating that the trial was adequately designed and powered to detect significant effects [18]. (See 'Oral naltrexone' above.)

It is not known whether discrepant findings between the European and US trials result from differences in sample composition, study methodology, or other factors. As examples of sample differences, the European trials on average enrolled subjects with more severe alcohol dependence treated in less controlled environments. The COMBINE study, conducted in the US, limited enrollment to individuals with at least four days of abstinence and no more than 21 days, while the European trials tended to enroll individuals abstinent for longer periods.

**Adverse effects** — Acamprosate is generally well tolerated at doses of up to 3 g/day. The most prominent adverse events are diarrhea, nervousness, and fatigue, which usually subside with continued use. Because acamprosate is excreted mostly unchanged by the kidneys, rather than the liver, it can be used safely in severely alcohol-dependent individuals with liver disease. Acamprosate dosage needs adjustment for renal insufficiency and is contraindicated in patients with renal failure.

## SECOND-LINE MEDICATIONS

**Disulfiram** — Disulfiram is an aversive agent that does not directly influence motivation to drink, but discourages drinking by causing an unpleasant physiologic reaction when alcohol is consumed. Clinical trials suggest that disulfiram is effective principally when taken routinely under supervised conditions.

Disulfiram inhibits aldehyde dehydrogenase and prevents the metabolism of alcohol's primary metabolite, acetaldehyde [31]. Drinking alcohol while taking disulfiram results in the accumulation of acetaldehyde in the blood, which causes unpleasant effects such as sweating, headache, dyspnea, lowered blood pressure, flushing, sympathetic overactivity, palpitations, nausea, and vomiting.

**Contraindications** — Contraindications to disulfiram include severe myocardial disease and/or coronary occlusion, psychosis, or known hypersensitivity to the medication or other thiuram derivatives [32,33]. Disulfiram is generally avoided in pregnant and nursing women. (See 'Treatment during pregnancy' below.)

**Administration** — Disulfiram is initially dosed at 500 mg/day for one to two weeks, followed by an average maintenance dose of 250 mg/day with a range from 125 to 500 mg based on the severity of adverse effects. The medication should not be used by patients with current alcohol intoxication. Patient education should address hidden forms of ethanol (eg, tonics and mouthwashes) and the duration of the drug's activity (up to 14 days after stopping).

**Efficacy** — A 2014 meta-analysis of two clinical trials with a total of 492 patients did not find a significant difference between disulfiram and placebo in return to any drinking or other primary substance use disorder (SUD) outcomes [19]. A systematic review found mixed results in one large trial and three smaller trials of disulfiram versus placebo for alcohol dependence [34]. The large study, a 52-week, multi-site trial of 605 US veterans, found disulfiram to be no more effective than placebo in maintaining abstinence or in time to first drink, but it may have reduced drinking days in a subgroup that drank during the study [35]. A high rate of noncompliance with medication was seen.

A subsequent study suggested that disulfiram is effective when the medication is taken routinely under supervised conditions. In a trial, 243 patients with alcohol dependence were randomly assigned to receive disulfiram, naltrexone, or acamprosate with regular supervision over a 12-week period [36]. Compared with patients taking naltrexone or acamprosate, patients taking disulfiram experienced a greater reduction in heavy drinking days and average weekly consumption, and a longer time to first drink. The relative benefits of disulfiram were less prominent in a subsequent, unsupervised treatment period of up to 52 weeks.

**Adverse effects** — Side effects of disulfiram are usually minor, including fatigue, mild drowsiness, headache, and dermatitis. Severe adverse reactions are rare, but include psychosis and hepatitis. Patients receiving disulfiram should be monitored for hepatotoxicity [37].

**Topiramate** — Topiramate, a sulfamate-substituted fructopyranose derivative, has been found to decrease alcohol use in individuals with alcohol dependence. It has not been approved by the US FDA for this indication. Topiramate has two principal mechanisms of action that may contribute to its anti-drinking effects:

- Antagonizing alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptors and kainate glutamate receptors [38].
- Facilitating inhibitory GABA(A)-mediated currents at non-benzodiazepine sites on the GABA(A) receptor [39].

Topiramate should be titrated up gradually over several weeks to minimize side effects. It is generally initiated at 50 mg/day and increased to a maximum dose of 150 mg twice daily [40].

A 2014 metaanalysis of three clinical trials with a total of 691 patients with alcohol dependence found topiramate to result decreased consumption compared with placebo on some primary SUD outcomes [19]. Four placebo-controlled trials have shown topiramate to decrease alcohol use among alcohol dependent individuals [41-44]. As an example, a multi-site trial found that topiramate reduced the percentage of heavy drinking days compared to placebo (43.8 versus 51.8 percent) among 371 men and women with alcohol dependence over 14 weeks [43]. Topiramate was more effective than placebo in percent days abstinent, number of drinks per day, and plasma gamma glutamyl transferase, a biological marker of alcohol intake. Trial dropout rates were higher in the topiramate group compared with placebo (39 versus 23 percent).

Three randomized trials comparing naltrexone to topiramate in patients with alcohol dependence found little difference between the drugs in primary outcomes [44-46].

**Adverse effects** — Adverse effects associated with topiramate include cognitive impairment (eg, word-naming difficulties), paresthesias, weight loss, headache, fatigue, dizziness, and depression. Adverse effects of topiramate are discussed in more detail separately. (See 'Treatment during

pregnancy' below and "Antiseizure drugs: Mechanism of action, pharmacology, and adverse effects", section on 'Topiramate'.)

**Gabapentin** — Clinical trials support the efficacy of gabapentin in treatment for DSM-IV alcohol dependence, though this has not been definitively established in a sufficiently large sample, and there is some concern about its abuse potential. As an example, a trial randomly assigned 150 adult patients with DSM-IV alcohol dependence to treatment with either 900 or 1800 mg/day of gabapentin or to placebo [47]. All patients received concurrent manual-based counseling. After 12 weeks, abstinence rates were higher in patients receiving gabapentin compared to patients receiving placebo (11 and 17 percent in the 900 and 1800 mg/day groups versus 4 percent in the placebo group, though confidence intervals for pair-wise results overlapped with placebo). Similar overall and pair-wise results were observed for rates of no heavy drinking. There were no serious adverse drug events.

Earlier clinical trials found evidence that gabapentin reduced alcohol consumption in patients with DSM-IV alcohol dependence, but these trials had small sample sizes and other methodologic limitations [48-50].

Gabapentin is well tolerated at low and moderate doses; sedation and dizziness can occur at higher doses. In our clinical experience and in published reports, gabapentin is subject to abuse by some patients treated for a SUD [51-55].

**Baclofen** — Clinical trials comparing baclofen (30 mg/day) with placebo in the treatment of alcohol dependence have found mixed results. Two trials with a total of 123 patients found that baclofen led to higher rates of abstinence compared with placebo [56,57], while a third trial with 80 patients found no significant differences in abstinence rates or in other primary outcomes compared with placebo [58]:

- A 12-week trial randomly assigned 80 subjects with alcohol dependence to receive baclofen (30 mg/day) or placebo; both groups received a low-intensity psychosocial intervention. No differences were seen in heavy drinking days, days abstinent, or time to relapse [58].
- A 12-week trial compared baclofen (10 mg three times daily) with placebo in 84 individuals with alcohol dependence and liver cirrhosis [56]. Individuals receiving baclofen were more likely to achieve and maintain abstinence compared with placebo (71 versus 29 percent; OR = 6.3, 95% CI 2.4-16.1). The cumulative duration of abstinence was also greater with baclofen (63 versus 31 days).
- A four-week trial comparing baclofen (30 mg/day) with placebo in 39 subjects with alcohol dependence found greater abstinence rates with baclofen compared with placebo (70 versus 21 percent) [57].

Preliminary evidence from a retrospective case series [59] and a secondary analysis of clinical-trial data [60] suggested that a higher dose of baclofen (60 mg/day) may be effective in alcohol dependence, but this requires further study in randomized trials.

Baclofen treatment was well tolerated in these trials, with no abuse liability. No serious adverse effects were seen, including hepatotoxicity, encephalopathy, or hyperammonemia. Mild-to-moderate side effects occurring at a greater rate than in the placebo group included nausea, vertigo, transient sleepiness, and abdominal pain [56,57].

**Nalmefene** — Nalmefene, an opioid antagonist, has been found to reduce drinking in patients with alcohol dependence using a targeted dosing strategy. Nalmefene has several potential advantages over naltrexone, including absence of dose-dependent liver toxicity, longer-acting effects, and more effective binding to central opiate receptors. Nalmefene is not available in some countries, including the US.

A 2014 metaanalysis of three clinical trials with a total of 608 patients with alcohol dependence found nalmefene to be superior to placebo on some primary SUD outcomes [19]. The three trials used a targeted dosing strategy (ie, taken as needed prior to encountering a high-risk situation) [61-63]. As an

example, a trial compared nalmefene using a targeted dosing strategy with placebo in 403 patients. Subjects were instructed to take 10 to 40 mg on days when drinking seemed imminent [63]. After 28 weeks, the mean number of heavy drinking days showed a greater reduction among individuals receiving nalmefene compared with placebo (44 versus 52 percent). Two of the trials used an 18-mg dose of nalmefene [61,62].

Mixed results have been found in trials of patients with alcohol dependence comparing daily oral nalmefene with placebo on the primary outcomes of relapse rates and heavy drinking days.

- Two 12-week trials in a total of 126 patients with alcohol dependence compared nalmefene 10 mg twice daily, 40 mg twice daily, and placebo [64,65]. A meta-analysis of the trials found nalmefene led to a greater reduction in relapse rate compared with placebo (relative risk [RR] 0.62, 95% CI 0.41-0.93) [66]. Outcomes did not differ by medication dose.
- A trial of 270 subjects with alcohol dependence compared patients treated with one of three doses of nalmefene (5, 20, or 40 mg) or placebo [67]. No differences in outcomes were found among any of the groups.

Adverse events occurring more commonly with nalmefene than placebo in this trial included nausea, insomnia, fatigue, dizziness, and malaise. In addition, fifteen subjects receiving nalmefene experienced psychosis or dissociation. Adverse events led to discontinuation of nalmefene among 16 percent of subjects and dose reduction among 31 percent.

**Selective serotonin reuptake inhibitors** — A meta-analysis of seven trials found that selective serotonin reuptake inhibitors (SSRIs) do not effectively treat alcohol dependence in patients who do not have a comorbid mental disorder [68]. These trials have several limitations: short time frames, a preponderance of male subjects, and use of non-standardized psychosocial interventions.

Studies suggest that SSRIs may be effective in more homogenous subgroups:

- A meta-analysis found that SSRIs and other antidepressants can reduce intake when alcohol dependence and depression co-occur [69]. (See "Co-occurring schizophrenia and substance use disorder: Epidemiology, pathogenesis, clinical manifestations, course, assessment and diagnosis".)
- Preliminary evidence suggests that subtypes of alcohol dependence may respond differently to serotonergic drugs, with more favorable outcomes seen in the group characterized by a later age of onset, a preponderance of psychosocial morbidity, and low familial loading. Lesser response to these agents, or even increased alcohol consumption, has been observed among individuals with an earlier-onset subtype, which has high familial loading and a range of impulsive or antisocial traits suggesting careful assessment and follow-up when using SSRIs in alcohol-dependent individuals [70-73].

(See "Serotonin-norepinephrine reuptake inhibitors (SNRIs): Pharmacology, administration, and side effects".)

**Ondansetron** — Early-onset alcohol dependence (onset of problem drinking prior to age 25 years) differs from late-onset alcohol dependence (onset of problem drinking later than age 25 years) by having associations with greater serotonergic abnormality and antisocial behaviors. Ondansetron, a serotonin 5-HT<sub>3</sub> receptor antagonist used to treat chemotherapy-induced nausea, does not appear to effectively treat all patients with alcohol dependence, but clinical trials suggest that the drug is selectively effective in two clinical subgroups [74-77]:

- Patients with early-onset subtype of alcohol dependence
- Patients with a specific genetic variant of the serotonin transporter (5-HTT) gene. (See 'Neurobiology' above.)

Clinical trials of ondansetron in samples of patients with alcohol dependence (undifferentiated, early/late, and varied genotypes, respectively) are described below:

- A six-week randomized trial of 71 men with nonsevere alcohol dependence (not differentiated by subtype) found no significant difference between ondansetron and placebo in alcohol consumptions [74].
- A 12-week randomized trial of 271 individuals with alcohol dependence, which differentiated subjects by age of onset of alcohol dependence, found that ondansetron was more effective than placebo on multiple measures of alcohol intake for those with early-onset of the disorder, but not late-onset [75]. No severe adverse events occurred in the trial; no difference was seen between the ondansetron and placebo groups in rates of mild-to-moderate adverse events.
- A 12-week randomized trial compared ondansetron (4 mcg/kg intravenously injected twice daily) with placebo in 283 individuals classified into one of three categories by genotype: the LL, LS, and SS genotypes in the promoter region of the serotonin transporter (5-HTT) gene [77]. Individuals with the LL genotype who received ondansetron had a lower mean number of drinks per drinking day (−1.62) and a higher percentage of days abstinent (11.27 percent) than those who received placebo. Individuals with both the LL and TT genotypes who received ondansetron reported fewer drinks per drinking day (−2.63) and a higher percentage of days abstinent (16.99 percent).

**Adverse effects** — Adverse effects associated with ondansetron include diarrhea, headache, and fever. Ondansetron prolongs the QT interval in a dose-dependent manner, and should be avoided in patients with underlying heart conditions, such as congenital long QT syndrome, or taking other medications that lead to QT prolongation [78].

**OTHER MEDICATIONS** — Medications currently under study for alcohol use disorder include other anticonvulsants, antipsychotics, dopamine antagonists, CRF antagonists, neuropeptide Y antagonists, varenicline, and the cannabinoid receptor antagonist rimonabant.

**COMBINING MEDICATIONS** — Combining medications, particularly those with different mechanisms of action, offers the possibility of more effective treatment for patients who do not respond adequately to an individual agent.

Two trials compared the combination of oral naltrexone and acamprosate, finding mixed results. In a trial of 160 individuals with alcohol use disorder, the group receiving naltrexone and acamprosate experienced fewer relapses and a longer time to first drink than those receiving acamprosate alone. However, the combined medications were no more effective than naltrexone alone [79]. The COMBINE Study did not find an advantage to combined naltrexone-acamprosate treatment compared with either the individual agents or placebo [18]. (See 'Oral naltrexone' above.)

A small, eight-week trial of the combination of ondansetron and naltrexone for early-onset alcohol use disorder led to reduced drinking and reduced levels of carbohydrate-deficient transferrin (a marker of alcohol use) compared with placebo. Combined treatment was not compared with either drug individually [80,81].

Two trials found the combination of naltrexone and sertraline (an SSRI) to be no more effective than naltrexone alone in maintaining abstinence among individuals with alcohol use disorder [82,83].

**COMPARING MEDICATION WITH PSYCHOSOCIAL TREATMENTS** — There are no clinical trials that directly compare medications to psychosocial interventions in alcohol dependence or alcohol use disorder. (See 'Psychosocial treatment of alcohol use disorder'.)

**COMBINING MEDICATION WITH PSYCHOSOCIAL TREATMENTS** — The evidence is mixed as to whether combining medication with a structured psychosocial intervention leads to better outcomes for alcohol use disorder than medication alone (see 'First-line medications' above and 'Acamprosate' above and 'Psychosocial treatment of alcohol use disorder').

- The COMBINE Study compared naltrexone, acamprosate, a psychosocial intervention, combination naltrexone-psychosocial treatment, acamprosate-psychosocial treatment, and placebo in 1383 patients with alcohol use disorder [18]. The psychosocial intervention integrated aspects of cognitive-behavioral therapy (CBT), 12-step programs, motivational interviewing, and support system involvement. No differences were seen with either medication combined with psychosocial treatment compared with the respective medication alone or the psychosocial treatment alone.
- An earlier, smaller study provided limited evidence suggesting combined naltrexone and CBT were more effective than naltrexone alone [84].

**TREATMENT SELECTION** — Limited data are available on comparative effectiveness, drug characteristics, treatment goals, and predictors of response that can inform clinicians' selection among treatments for alcohol use disorder. The suggestions that follow are based on these data and our clinical experience.

- We suggest that patients with moderate to severe alcohol use disorder initially be offered a choice of medication or an evidence-based psychosocial intervention such as cognitive behavioral therapy (CBT). There are no trials comparing the two, and findings are mixed as to whether the combination of both is more effective than either intervention alone. (See 'Comparing medication with psychosocial treatments' above and 'Combining medication with psychosocial treatments' above.)
  - Patients with the mild subtype of alcohol use disorder who are currently drinking heavily and risk serious consequences can be considered for these treatments on a case-by-case basis. Data on the efficacy of these interventions are typically not generalizable to patients with the mild subtype.
- For patients who do not achieve remission or an adequate reduction in heavy drinking with medication or a psychosocial intervention, we recommend combining modalities if the first was partially effective or switching modalities if the first was ineffective. (See 'Combining medication with psychosocial treatments' above.)
- When medication is used for alcohol use disorder, we suggest first-line treatment with naltrexone for most patients over other medications. Metaanalyses of trials comparing acamprosate with naltrexone found no significant difference between them for return to any drinking or return to heavy drinking. An earlier, 2006 meta-analysis concluded that acamprosate may be more effective for maintenance of abstinence (compared with placebo, relative risk [RR] 0.84, 95% CI 0.78-0.91), while naltrexone was more effective for reduction of heavy drinking (compared with placebo, relative risk [RR] 0.80, 95% 0.71-0.91) [85]. (See 'Acamprosate' above and 'First-line medications' above.)

Predictors of therapeutic response to naltrexone include family history of alcohol use disorder and strong cravings for alcohol [86]. (See 'First-line medications' above.)

Predictors of therapeutic response to acamprosate include increased levels of anxiety, physiological dependence (ie, severe symptoms of withdrawal), negative family history, late age of onset, and female gender [87]. (See 'Acamprosate' above.)

Depot naltrexone is an option for treatment of patients likely to be nonadherent to daily oral medication. Nonadherence presents an impediment to effective pharmacotherapy for a substantial proportion of patients with alcohol use disorder in clinical trials and in practice. As an example, 37 percent of patients taking naltrexone in a meta-analysis of clinical trials prematurely discontinued the medication during the study [66]. (See 'Depot naltrexone' above.)

For pharmacotherapy of an alcohol use disorder in patients with acute hepatitis, liver enzymes greater than three to five times normal, or liver failure, we suggest acamprosate over other

- medications. Baclofen would be a reasonable alternative. Naltrexone has been associated with hepatotoxicity, particularly at high doses, and acamprosate has been shown to be safe for patients with alcohol use disorder and severe liver disease. Baclofen appears safe and effective for patients with alcohol use disorder and cirrhosis. (See First-line medications above and Acamprosate above and Baclofen above.)
- Acamprosate should also be considered as an alternative to naltrexone for patients under concurrent treatment with opioids. (See 'Acamprosate' above.)
- Acamprosate is not indicated for the induction of abstinence in actively drinking patients. (See 'Acamprosate' above.)
- For patients with alcohol use disorder for which naltrexone and acamprosate are ineffective or not indicated, other options with evidence supporting efficacy include disulfiram, topiramate, gabapentin, baclofen, and ondansetron.
  - Disulfiram should not be used unless the treatment goal is to maintain abstinence. Because this medication is associated with particularly high rates of nonadherence, use should be limited to highly motivated patients and those who take medication under supervision. (See 'Disulfiram' above.)
  - Serotonergic agents may be more effective when used selectively for subtypes of alcohol use disorder. Preliminary evidence suggests that SSRIs may be more effective for a late-onset subtype and comorbid depression. Ondansetron, a serotonin antagonist, may be more effective for patients with an early-onset disorder and for patients with a specific genetic variant of the serotonin transporter (5-HTT) gene. (See 'Selective serotonin reuptake inhibitors' above and 'Ondansetron' above.)

**TREATMENT DURING PREGNANCY** — There is a paucity of data on the safety of pharmacologic therapies for alcohol use disorder in pregnant women. In weighing risks and benefits of prospective treatment, one should also consider the harmful effects of alcohol to the mother and to the developing fetus. (See "Alcohol intake and pregnancy".)

If feasible, treatment of pregnant women with substance abuse disorders should be managed by clinicians with specialized expertise in this area. Potential issues with medications used for alcohol use disorder include the following [88,89]:

- Naltrexone is used in pregnancy more commonly than are other medications for alcohol use disorder because of the absence of known, harmful effects; this decision should be made cautiously due to the absence of well-controlled studies of any of the medications in humans.
- Disulfiram may harm the developing fetus by increasing levels of acetaldehyde. In addition, the physiologic reaction between disulfiram and ethanol in the mother presents a potential risk to the fetus. For these reasons, disulfiram is rarely used in pregnancy.
- Opiate antagonists such as naltrexone are used with caution in pregnancy due to their potential to induce a withdrawal syndrome, harmful to the fetus, among patients surreptitiously taking opiates.
- Acamprosate is teratogenic in animal studies. There are no adequate studies of pregnant women with fetal exposure.
- There is an increased risk for the development of cleft lip and/or cleft palate (oral clefts) in infants born to women treated with topiramate during pregnancy, but this occurrence is rare [90].
- Topiramate has been found to be teratogenic in animal studies. It crosses the placenta in humans. A preliminary report on 203 prospectively followed pregnancies exposed to topiramate found a high rate of major congenital malformations [91]. (See "Risks associated with epilepsy and pregnancy".)

(See ["Overview of substance misuse in pregnant women"](#) and ["Alcohol intake and pregnancy"](#) and ["Management of moderate and severe alcohol withdrawal syndromes"](#).)

**INFORMATION FOR PATIENTS** — UnToDate offers two types of patient education materials. "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5<sup>th</sup> to 6<sup>th</sup> grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10<sup>th</sup> to 12<sup>th</sup> grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see ["Patient information: Alcohol use — when is drinking a problem? \(The Basics\)"](#))
- Beyond the Basics topics (see ["Patient information: Alcohol use — when is drinking a problem? \(Beyond the Basics\)"](#))

## SUMMARY AND RECOMMENDATIONS

- Medications to treat alcohol use disorder are needed despite the availability of effective psychosocial interventions. As many as 70 percent of individuals relapse after psychosocial treatment alone. (See ["Introduction"](#) above.)
- Pharmacologic treatment of alcohol abuse use disorder has mostly focused on altering the reinforcing effects of alcohol use. Many available or promising medications appear to act by modulating the function of opioids, glutamate (with or without GABA), or serotonin. (See ["Neurobiology"](#) above.)
- Goals for treatment include abstinence, the traditional objective of alcohol treatment, or reduction of heavy drinking, a measure of alcohol intake strongly related to negative life consequences. (See ["Treatment principles and overview"](#) above.)
- We suggest that patients with moderate to severe alcohol use disorder initially be offered a choice of medication or an evidence-based psychosocial intervention, or both (**Grade 2C**). Patients with the mild subtype, current heavy drinking, and risk of serious consequences can be considered for medication treatment on a case-by-case basis. All patients should receive some psychosocial treatment. (See ["Indications"](#) above and ["Psychosocial treatment of alcohol use disorder"](#) and ["Treatment selection"](#) above.)

Patients who do not achieve remission or an adequate reduction in heavy drinking should receive a trial of the other modality or a combination of modalities. (See ["Treatment selection"](#) above and ["Combining medication with psychosocial treatments"](#) above.)

- For patients taking medication, we suggest [naltrexone](#) for most patients with alcohol use disorder over other medications (**Grade 2B**). Depot naltrexone should be used when there is a significant risk of nonadherence with daily administration; patients should be monitored for injection site reactions. Naltrexone is not appropriate for patients with liver disease or who are taking opioids. (See ["First-line medications"](#) above.)
- For pharmacotherapy of an alcohol use disorder in patients with acute hepatitis, liver enzymes greater than three to five times normal, or liver failure, we suggest [acamprosate](#) over other medications (**Grade 2C**). [Baclofen](#) would be a reasonable alternative. The evidence for the efficacy of acamprosate is mixed. Its use may be considered for individuals with liver disease or those who do not respond to other medications. (See ["Acamprosate"](#) above.)

- For patients with alcohol use disorder for which naltrexone and acamprosate are ineffective or not indicated, other options with evidence supporting efficacy include disulfiram, topiramate, gabapentin, baclofen, and ondansetron. (See 'Second-line medications' above.)
  - Use of disulfiram should be reserved for individuals who are highly motivated to maintain abstinence, and are either treatment adherent or take the medication in a supervised setting. (See 'Disulfiram' above.)
  - In treating alcohol use disorder with topiramate, care must be taken to increase the dose slowly to avoid adverse events including cognitive impairment (eg, word-naming difficulties), paresthesias, and weight loss. (See 'Topiramate' above.)
  - Clinical trials of baclofen in alcohol use disorder have led to mixed results. Larger randomized trials are needed to determine its efficacy. (See 'Baclofen' above.)
  - Targeted dosing of nalmefene has been found to improve outcomes in alcohol use disorder in clinical trials; trials of daily dosing have led to mixed results. (See 'Nalmefene' above.)

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