Alcohol use disorder: Pharmacologic management

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INTRODUCTION

Alcohol use disorders are among the most prevalent of all substance use disorders worldwide. The single year prevalence globally has been estimated to be over 100 million individuals [1]. Additionally, nearly 3 million deaths (5.3 percent of all deaths globally) have been attributed to alcohol in a single year [2].

Most clinical trials of medication efficacy for alcohol use disorder studied recently abstinent individuals with an American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) diagnosis of alcohol dependence. Applying these findings to individuals diagnosed under the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) is imprecise, but the most closely comparable group of individuals are those with alcohol use disorder, moderate to severe subtype (ie, individuals with four or more symptoms within a 12-month period).

Pharmacologic treatment of alcohol use disorder has focused on altering the reinforcing effects of alcohol use. Medication development has focused on several neurotransmitter systems that mediate reinforcement including opioid, glutamate, gamma-aminobutyric acid, and serotonin systems.

Several medications can be used to treat alcohol use disorder, leading to reduced heavy drinking and increased days of abstinence [3]. These outcomes likely reduce the overall risk associated with alcohol use disorder despite total abstinence not being achieved.

This topic reviews the pharmacotherapy for treatment of alcohol use disorder. The epidemiology, pathogenesis, clinical manifestations, assessment, and diagnosis of risky drinking and alcohol use disorder, as well as psychosocial treatments for the disorder, are discussed separately. Other topics related to alcohol use disorder including the management of withdrawal and nutritional issues are also reviewed separately.

- (See "Risky drinking and alcohol use disorder: Epidemiology, clinical features, adverse consequences, screening, and assessment".)
- (See "Screening for unhealthy use of alcohol and other drugs in primary care".)
- (See "Brief intervention for unhealthy alcohol and other drug use: Efficacy, adverse effects, and administration".)
- (See "Alcohol withdrawal: Ambulatory management".)
- (See "Management of moderate and severe alcohol withdrawal syndromes".)

INDICATION FOR PHARMACOTHERAPY

Medication treatment of alcohol use disorder has been shown to be effective in patients with moderate to severe subtypes of the disorder. Medication should be prescribed in conjunction with psychosocial interventions, though it should not be withheld if patients do not participate in or adhere to them. (See "Alcohol use disorder: Treatment overview", section on 'Moderate or severe disorder'.)

In contrast, medication treatment has not been extensively studied in patients with mild subtype of alcohol use disorder. In these patients, we suggest initial treatment with psychosocial interventions rather than with medication. (See "Alcohol use disorder: Treatment overview", section on 'Mild disorder' and "Alcohol use disorder: Psychosocial management".)

An algorithm describes our approach to the pharmacologic management of alcohol use disorder (algorithm 1).

FIRST-LINE TREATMENT

Suggested first- and second-line agents used in the treatment of alcohol use disorder can be found on the associated table (table 1).

Naltrexone — For most newly diagnosed patients with moderate or severe alcohol use disorder, we suggest initial treatment with naltrexone. Naltrexone is our preferred choice due to

its preferable dosing schedule and the ability to begin treatment for alcohol use disorder while the individual is still drinking.

Naltrexone exerts its principal pharmacologic effects through blockade of the mu-opioid receptor. Endogenous opioids modulate alcohol's reinforcing effects [4,5]. Naltrexone also modifies the hypothalamic-pituitary-adrenal axis to suppress ethanol consumption [6].

- **Contraindications** – Naltrexone should be avoided in individuals using opioids or prescribed opioids for pain management, as well as in those with acute hepatitis or hepatic failure; in such patients, the alternative first-line treatment, acamprosate is appropriate.

- **Formulations** – Naltrexone can be taken orally or administered in a long-acting injectable (LAI) form. Both oral and long-acting dosing have demonstrated efficacy compared with placebo. Comparative studies are limited and have come to different conclusions regarding comparative efficacy [7-9].

  - **LAI naltrexone** – For most patients treated with medication for alcohol use disorder, the decision to begin oral versus intramuscular (IM) is based on patient preference. We typically prefer starting IM naltrexone to ensure adherence. However, some may prefer to start with oral medication (ie, to see if side effects emerge or liver enzymes are affected), before committing to a longer course of treatment. Depot preparations of naltrexone may improve adherence by reducing the frequency of medication administration from daily to monthly. However, they do require an injection visit. Some patients may adhere better to daily medication whereas others may be willing to attend monthly visits. Additionally, a steady state of medication level is achieved with LAI naltrexone. This may avoid peak effects that might exacerbate adverse events [10].

    LAI naltrexone is given as an IM injection of 380 mg every four weeks to the gluteal area. Common adverse events observed among individuals receiving LAI naltrexone included nausea (33 percent), fatigue (20 percent), and decreased appetite (13 percent).

    The US Food and Drug Administration has reported 196 cases of serious injection site reactions from postmarketing surveillance including induration, cellulitis, hematoma, abscess, and necrosis. Females appear to be at higher risk for this reaction. Patients should report injection-site pain, swelling, bruising, pruritus, or redness, and seek medical attention if symptoms are not improving after one week. Liver enzymes should be monitored within several weeks of initiating treatment and then every six months during ongoing treatment.

LAI naltrexone appears to be superior to placebo in reducing drinking and heavy drinking among adults with alcohol use disorder [11,12]. For example, in a meta-analysis, individuals with alcohol use disorder treated with LAI naltrexone had fewer days of drinking per month compared with individuals receiving placebo (five trials, n = 314; weighted mean difference -2.0, 95% CI -3.39 to -0.61) [12]. Additionally, individuals treated with LAI naltrexone had fewer heavy drinking days per month (defined as four or more drinks/day in females; five or more drinks/day in males) than those in placebo group (seven trials, n = 881; weighted mean difference -1.2, 95% CI -2.1 to -0.23).

- **Oral naltrexone** – Our practice is to start oral naltrexone at 50 mg per day and monitor for side effects. While the usual dose of oral naltrexone is 50 mg/day, some trials have used up to 100 mg/day [13]; some also begin with 25 mg daily for several days and then increase the dose to 50 mg when the medication is tolerated well. Trials generally have included efforts such as group and individual psychotherapy [14].

  Targeted (as needed) dosing may be a useful strategy for promoting adherence in young individuals who often prefer to take medication on an as needed basis [15,16]. While we typically prescribe naltrexone for daily use, targeted dosing may be an effective alternative or supplement to daily dosing. In one trial including 140 young adults with heavy drinking (ie, four or more heavy drinking days over the past four weeks), the use of targeted naltrexone was found to reduce the likelihood of intoxication by nearly 23 percent versus placebo [15].

  Meta-analyses of clinical trials for alcohol dependence have found oral naltrexone to reduce alcohol consumption compared with placebo [17-19]. As an example, a meta-analysis of 50 randomized trials with 7793 alcohol dependent participants found that compared with placebo, naltrexone reduced the risk of a return to heavy drinking, 51 versus 61 percent (relative risk 0.83, 95% CI 0.76-0.90) and decreased total drinking days by approximately 4 percent. Any drinking was decreased by 5 percent [17].

  Side effects of oral naltrexone are nausea, headache, and dizziness, which subside with continued use.

  Liver enzymes should be monitored within several weeks of initiating treatment and then every six months during ongoing treatment. Fivefold elevation in liver enzymes occurred in 11 of 614 individuals who received naltrexone in the COMBINE study [13]. Enzyme levels returned to baseline after discontinuation of medication in the nine individuals who had stopped drinking and returned for follow-up. Elevations in liver enzymes are therefore largely attributable to heavy drinking; in a large safety study

(865 patients), liver enzymes did not differ from a comparison group not taking naltrexone [20].

Acamprosate — Acamprosate is an effective alternative to naltrexone and is our first choice in patients with contraindications to naltrexone, including those who are using opioids or prescribed opioids, or in those with advanced liver disease. For patients who have minimal to no response to naltrexone as first line of treatment, we stop naltrexone and treat with acamprosate as our second choice (unless contraindicated). In individuals with a partial or insufficient response to naltrexone we augment with acamprosate; however, we do this less frequently as we are sensitive to avoiding polypharmacy.

Acamprosate's principal antidrinking neurochemical effect has been attributed to the modulation of glutamate neurotransmission at metabotropic-5 glutamate receptors [21].

- **Contraindications** – Acamprosate is contraindicated in individuals with severe renal dysfunction (creatinine clearance ≤30 mL/min).
- **Administration** – We begin treatment with acamprosate when abstinence is achieved and, typically, maintain treatment during return to use. The usual dose for acamprosate is 666 mg three times daily. However, in individuals with moderate renal dysfunction (creatinine clearance 30 to 50 mL/min) an initial dose of 333 mg three times daily is recommended. Additionally, in individuals with a body weight <60 kg we typically initiate treatment at a lower dose (eg, 333 mg twice daily).
- **Efficacy** – Meta-analyses have shown that acamprosate is effective in maintaining abstinence in individuals with alcohol use disorder who were recently detoxified from alcohol use [19,22,23]. As an example, in a meta-analysis of 18 studies including nearly 2300 individuals who were recently detoxified from alcohol use, acamprosate increased the likelihood of continuous abstinence versus placebo at 12 months (odds ratio 1.86, 95% CI 1.49-2.33) [23].
- **Adverse effects** – The most prominent adverse events of treatment with acamprosate include diarrhea, nervousness, and fatigue. These usually subside with continued use. Because acamprosate is excreted mostly unchanged by the kidneys, rather than the liver, it can be used safely in alcohol-dependent individuals with liver disease.

SPECIFIC PATIENT POPULATIONS

A number of factors such as co-occurring disease, patient motivation, and treatment goals can influence the initial choice of medication for alcohol use disorder.

Patients with co-occurring hepatic disease — In patients with acute hepatitis, liver failure, or in patients with liver enzymes ≥3 to 5 times normal, we suggest initial treatment with acamprosate. Naltrexone is contraindicated in these patients.

Patients with opioid use disorder — For patients with alcohol use disorder with comorbid opioid use disorder but without other contraindications (such as severe hepatic disease) we use naltrexone to treat both conditions after a sufficient time has elapsed since opioid exposure (see "Opioid use disorder: Pharmacologic management", section on 'Naltrexone: Opioid antagonist'). Naltrexone should be avoided in individuals currently using opioids.

Alternatively, since opioid agonists are often the medication of choice for opioid use disorder, the comorbid alcohol use disorder can be treated with acamprosate or other medications. (See 'Patients requiring additional therapy' below.)

Patients with clinically indicated opioid use — For patients with alcohol use disorder who are taking prescribed opioid medication, we suggest treatment with acamprosate rather than naltrexone. Naltrexone, an opioid antagonist cannot be given to patients needing to continue opioids (eg, for pain control or to treat opioid use disorder).

Pregnancy — The treatment of pregnant women with substance use disorder should be managed by clinicians with specialized expertise in this area. Psychosocial treatments are prioritized as there is a paucity of data on the safety of pharmacologic therapies for alcohol use disorder in pregnant individuals.

If abstinence is not achieved without the use of medications, the risks of continued heavy drinking likely outweigh the possible adverse effects of medication. In weighing risks and benefits of prospective treatment, one should consider potentially harmful effects of alcohol to the mother and to the developing fetus, with alcohol a known teratogen and the most common cause of congenital anomaly in the United States. One small study suggested no clear association between exposure to acamprosate with poor maternal or neonatal health outcomes [24]. Acamprosate may also be favored because opioids may be desired around delivery. However, naltrexone has been used more widely for substance use disorder during pregnancy.

The American Psychiatric Association guidelines for the pharmacologic treatment of patients with alcohol use disorder, state that for pregnant or breastfeeding women with alcohol use disorder, pharmacologic treatments should not be used unless treating acute alcohol withdrawal or a co-occurring disorder [25].

Topics related to substance use, including alcohol use during pregnancy, are reviewed separately [26,27]. (See "Substance use during pregnancy: Screening and prenatal care" and "Alcohol intake and pregnancy".)

Patients with nonabstinence goals — We treat patients whose treatment goal is reduction of alcohol use with naltrexone as naltrexone can be initiated while the patients is still drinking. Studies of acamprosate have generally enrolled patients who have abstained prior to starting medication.

PATIENTS REQUIRING ADDITIONAL THERAPY

For individuals who have not responded adequately to either naltrexone or acamprosate we suggest the following therapeutic options.

Dose adjustments — Trials have not supported using higher doses in individuals who have not responded sufficiently to initial therapy. Despite this, clinicians will often try a higher dose of medication if a lower dose does not reduce drinking sufficiently. A plausible rationale for this practice is that a higher dose might compensate for missed doses. Additionally, a higher dose may have a greater perceived effect by an individual patient. In one small study, a higher level of beta-naltrexone correlated with less alcohol craving [28]. This may provide a rationale for using higher dose of naltrexone (ie, 100 mg) in patients with persistent craving.

Subsequent medication trials — There are limited empirical data supporting augmenting options for suboptimal response to initial medication in the treatment of alcohol use disorder. Our practice is generally to switch from one medication to another in order to minimize polypharmacy. (See 'Combining medications' below.)

For patients who do not respond to naltrexone or acamprosate (or if they are contraindicated), our next choices are disulfiram or topiramate (unless contraindicated). We choose between these based on clinical presentation. For example, in patients who are motivated towards abstinence, and in cases where significant social support is available, we favor treatment with disulfiram. In patients with a seizure disorder, we favor topiramate (table 1).

Disulfiram — Clinical trials suggest that disulfiram is effective principally when taken under supervised conditions. Disulfiram is an aversive agent that does not directly influence motivation to drink, but discourages drinking by causing an accumulation of alcohol's primary metabolite, acetaldehyde. This accumulation causes unpleasant effects such as sweating, headache, dyspnea, lowered blood pressure, flushing, sympathetic overactivity, palpitations, nausea, and vomiting [29].

- **Administration** – Disulfiram is initially given at 250 to 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.

  Forty-eight hours of total abstinence is needed prior to starting disulfiram. Patient education should address "hidden" forms of ethanol (eg, tonics and mouthwashes) and also the duration of the drug's activity (up to 14 days after stopping).

  Supervised dosing is not required for this medication, as highly motivated patients likely do not require this level of oversight. Prior research, however, has suggested that patients who do have the benefit of supervised disulfiram dosing, via strong social support, tend to fare substantially better than controls with regards to sustained abstinence [30].

- **Efficacy** – Several blinded randomized controlled trials have failed to demonstrate a treatment effect for disulfiram according to one meta-analysis [30]. However, investigators have argued that the unique deterrent effect of disulfiram necessitates open-labeled studies to investigate its efficacy [30-32]. Meta-analysis of 17 open-labeled studies found a medium to large treatment effect for disulfiram over controls, which included both placebo and medication comparators (naltrexone and acamprosate) on abstinence outcomes (Hedges' g = 0.7, 95% CI 0.46-0.93) [30]. However, the ability to draw conclusions from this analysis is limited by substantial heterogeneity among trials in regard to patient populations, measured outcomes, and co-treatments; in addition, several studies were judged to have possible risk of bias.

- **Disulfiram reaction** – Reactions to disulfiram are self-limited. However, some individuals taking disulfiram who drink alcohol or alcohol-containing products can have a severe reaction to the combination. The severity and duration of the reaction depends on the amount of alcohol ingested. The reaction may last for several hours or up to a day.

  Individuals may present with symptoms such as chest pain, confusion, headache, and vomiting that require further evaluation for myocardial infarction and other etiologies. Once myocardial infarction is excluded in patients with chest pain, treatment is primarily supportive (antiemetics for vomiting; Trendelenburg positioning and intravenous fluids for orthostatic hypotension; diphenhydramine for flushing).

  Fomepizole has been suggested for life-threatening symptoms of acetaldehyde in patients with severe presentations. Fomepizole (4-methylpyrazole), administered as a single intravenous 7.5 mg/kg dose, blocks alcohol dehydrogenase and has been shown to reverse disulfiram reactions in a small case series of patients with nonspecific

electrocardiogram changes with chest pain who are unresponsive to fluid administration and norepinephrine [33,34].

- **Contraindications** – Contraindications to disulfiram include clinically significant coronary artery disease, psychosis and known hypersensitivity to the medication or other thiuram derivatives [35,36].

- **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. Individuals receiving disulfiram should be monitored for hepatotoxicity several weeks after initiating treatment and then every six months if treatment with disulfiram continues [37].

Topiramate — Topiramate is our preferred choice of medications in patients who have a seizure disorder that would be appropriately treated with it, and who have failed initial treatment with naltrexone or acamprosate.

Topiramate, an anticonvulsant medication with pharmacological properties including blocking of voltage-dependent sodium channels, potentiation of gamma-aminobutyric acid mediated transmission and antagonism of glutamate receptors, has been found to decrease alcohol use in individuals with alcohol use disorder.

- **Administration** – Topiramate is initiated at a dose of 25 mg daily and can be slowly titrated up to a maximum dose of 300 mg/day, over eight weeks. A titration schedule is shown in the table (table 2).

- **Efficacy** – In clinical trials, topiramate reduces alcohol consumption compared with placebo [17,38,39]. A meta-analysis of seven clinical placebo-controlled trials with a total of 1125 individuals with alcohol dependence demonstrated efficacy for topiramate with higher rates of abstinence and lower rates of heavy drinking, but similar measure of alcohol craving [38]. The specific outcome measures used varied across studies, but overall, the effects were judged to be small to moderate.

- **Adverse effects** – Adverse effects associated with topiramate include cognitive impairment (eg, word-finding difficulties), paresthesias, weight loss, headache, fatigue, dizziness, and depression. Many of these are intolerable to a relatively small but significant proportion of individuals. (See "Antiseizure medications: Mechanism of action, pharmacology, and adverse effects", section on 'Topiramate'.)

Gabapentin — Gabapentin may be a reasonable option for patients who may have previously failed a first-line option, particularly if gabapentin was used during a successful ambulatory detoxification.

Clinical trials testing the efficacy of gabapentin at various doses from 900 to 3600 mg have found mixed results in treatment for alcohol use disorder [40-42]. In a meta-analysis of seven placebo-controlled randomized controlled trials, gabapentin was effective only on a single drinking outcome – percent of heavy drinking days (g = 0.64, 95% CI 0.06-1.22) [43]. In one small trial, the efficacy of gabapentin in reducing heavy drinking appeared more pronounced in those with withdrawal symptoms compared with those without [42]. (See "Alcohol withdrawal: Ambulatory management", section on 'Very mild withdrawal (CIWA-Ar <10)'.)

One important risk of gabapentin is its addictive potential.

Combining medications — Combining medications in the treatment of alcohol use disorder has not been supported by trials. Theoretically, the combination of medications with different mechanisms of action offers the possibility of more effective treatment for patients who do not respond adequately to an individual agent. As an example, if some effect is achieved with naltrexone, adding acamprosate could have added effect in an individual.

However, randomized clinical trials have thus far not found medication combinations (naltrexone/acamprosate [13] and naltrexone/sertraline [44,45]) to be more effective than the individual medications. In most cases, our practice is to switch from agent to another rather than adding a second agent.

Agents with limited empirical support — Other medications with few data to support their use are discussed briefly below. Due to limited empirical support in the treatment of alcohol use disorder, we cannot recommend them as first- or second-line agents until further studies support their efficacy.

- **Nalmefene** – Nalmefene, an opioid antagonist, has been found to reduce drinking in individuals with alcohol use disorder using a targeted dosing strategy; however, the methodological rigor of the trials have been questioned [46,47]. 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 approved for treatment of alcohol use disorder in the European Union. It is available in the United States as treatment for opioid overdose [17,48-51].

- **Selective serotonin reuptake inhibitors (SSRIs)** – 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, less psychosocial morbidity, and low familial loading. Additionally, SSRIs may be useful in treating individuals with depression and substance use disorder, commonly occurring comorbidities [52-55].

- **Ondansetron** – This is a serotonin 5-HT3 receptor antagonist used to treat chemotherapy-induced nausea. Ondansetron may be selectively efficacious in individuals with early-onset subtype of alcohol dependence (onset of problem drinking prior to age 25 years) and in individuals with family history of alcohol use disorder [56-58].

- **Varenicline** – While an earlier study reported on the potential for varenicline to reduce alcohol consumption in individuals with alcohol use disorder [59], this effect might be more limited [60] and in need of further validation. Some studies suggest that varenicline treatment may be associated with reduced drinking in patients with alcohol addiction who smoke and in patients with alcohol use disorder and depression [61,62].

- **Psilocybin** – Psilocybin administered in combination with psychotherapy appears to decrease the number of heavy drinking days in individuals with alcohol use disorder. In a trial, 95 subjects with alcohol use disorder were randomly assigned to two day-long medication sessions (week 4 and week 8) with psilocybin or diphenhydramine (active control), each in addition to 12 weeks of manualized psychotherapy [63]. Over the 32-week follow-up period, subjects in the psilocybin group reported a lower percentage of heavy drinking days than those in the diphenhydramine group (9.7 versus 23.6, respectively; mean difference 13.86, 95% CI 3.0-24.7). Furthermore, subjects in the psilocybin group had fewer mean drinks per day than the diphenhydramine group (1.2 versus 2.3, respectively; mean difference 1.1, 95% CI 0.27-0.92). No serious adverse events were reported among either group. Although psilocybin is classified as a Schedule I controlled substance in the United States (no accepted medical use and high potential for abuse), these data suggest that further evaluation of psilocybin for alcohol use disorder management may be warranted.

- **Others** – Baclofen [64,65], prazosin, and doxazosin (alpha-1 antagonists) [66] also have limited data to support their use.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Alcohol use disorders

and withdrawal".)

INFORMATION FOR PATIENTS

UpToDate 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 5th to 6th 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 10th to 12th 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 individuals by searching on "patient info" and the keyword(s) of interest.)

- Basics topic (see "Patient education: Alcohol use — when is drinking a problem? (The Basics)")
- Beyond the Basics topic (see "Patient education: Alcohol use — when is drinking a problem? (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- **Indications for pharmacotherapy** – We prefer to treat individuals with moderate or severe alcohol use disorder with pharmacotherapy in conjunction with psychosocial intervention. However, for individuals with the mild subtype of the disorder, we prefer to begin with psychosocial intervention only (algorithm 1). (See 'Indication for pharmacotherapy' above.)
- **First-line treatment** – For most patients treated with medication for moderate or severe alcohol use disorder, we suggest initial treatment with naltrexone versus other medications available (**Grade 2C**). Naltrexone is preferred because of its once daily dosing and the ability to begin treatment while the individual is still drinking. (See 'Naltrexone' above.)

Acamprosate is an appropriate alternative to naltrexone for initial therapy and is our first-choice treatment for individuals who are using opioids or prescribed opioids as well as in those with advanced liver disease. (See 'Acamprosate' above and 'Patients with co-occurring hepatic disease' above.)

- **For specific patient populations** – Our initial choice of medications for patient specific populations depends on the comorbid condition. (See 'Specific patient populations' above.)
  - For co-occurring opioid use disorder, we prefer naltrexone (if not contraindicated) due to its potential effect in both disorder. (See 'Patients with opioid use disorder' above.)
  - For patients with clinically indicated opioid use, we prefer treatment with acamprosate. (See 'Patients with clinically indicated opioid use' above.)
  - For patients who are pregnant, we prefer psychosocial treatments as there is a paucity of data on the safety of pharmacologic therapies for alcohol use disorder. (See 'Pregnancy' above.)
  - For patients whose goal is reduction of alcohol use rather than abstinence, we prefer naltrexone. (See 'Patients with nonabstinence goals' above.)
- **Subsequent medication trials** – There are limited empirical data supporting augmenting options for suboptimal response to initial medication in the treatment of alcohol use disorder. Our practice is generally to switch from one medication to another in order to minimize polypharmacy. (See 'Subsequent medication trials' above.)

For patients who do not respond to naltrexone or acamprosate (or if they are contraindicated), our next choices are disulfiram or topiramate (unless contraindicated). (See 'Disulfiram' above and 'Topiramate' above.)

Other medication options with limited data supporting their use include gabapentin, selective serotonin reuptake inhibitors, ondansetron, and varenicline. We reserve their use for refractory cases. (See 'Agents with limited empirical support' above.)

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