JAMA Insights

Medications for Alcohol Use Disorder

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Alcohol use disorder (AUD), which affects 28 million individuals in the US, is a chronic, relapsing medical condition characterized by intense cravings, loss of control, and excessive alcohol use associated with serious social, occupational, and physical consequences. Excessive alcohol use is the most common cause of cirrhosis and increases the risk of cancers (eg, mouth, pharynx, larynx, esophagus, breast, colorectum, and liver), unintentional injuries, and heart disease.[1]

In addition to behavioral interventions, such as motivational interviewing and cognitive behavioral therapy, 3 medications are approved by the US Food and Drug Administration (FDA) for AUD: naltrexone, acamprosate, and disulfiram. Naltrexone and acamprosate are recommended as first-line treatments by the American Psychiatric Association,[2] while the US Department of Veterans Affairs recommends naltrexone and the anticonvulsant topiramate as first-line therapy.[3] Despite the established efficacy of medications for AUD, it is estimated that only 2.5% of US individuals with AUD are prescribed pharmacotherapy. Potential reasons for this treatment gap include clinical guidelines previously advising caution when prescribing medications for AUD to patients with known liver disease.

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Naltrexone

Naltrexone, which was FDA approved for AUD in 1995, is an opioid antagonist that blocks the pleasurable effects of alcohol mediated by pituitary release of β-endorphins when alcohol is consumed. Naltrexone is available as a once-daily pill or a monthly extended-release intramuscular injection (**Table**). A meta-analysis that included 19 double-blind randomized clinical trials (RCTs; N = 2875) of at least 12 weeks' duration reported that naltrexone 50 mg daily for AUD, compared with placebo, was associated with lower rates of return to heavy drinking (risk ratio [RR], 0.81 [95% CI, 0.72-0.90]), with a number needed to treat of 11.[4] In this meta-analysis, compared with placebo, injectable naltrexone (2 RCTs; N = 467) was associated with a reduction in the percentage of drinking days over the 30-day treatment period (weighted mean difference, −4.99 [95% CI, −9.49 to −0.49]). Common adverse effects included self-limited nausea (range, 2.5%-57.6% with naltrexone, 0%-47.1% with placebo) and dizziness (range, 2.9%-34.8% with naltrexone, 0%-20.6% with placebo) with both naltrexone formulations,[4] while injection site reactions occurred in up to 5.6% of patients with injectable naltrexone.[5] Postmarketing studies have found naltrexone is safe in patients with Child-Pugh class A or B cirrhosis. As an opioid antagonist, naltrexone should not be used in patients concurrently taking opioids.[5]

Acamprosate

Acamprosate, FDA approved for treatment of AUD in 2004, is believed to stabilize the neurochemical imbalance in γ-aminobutyric acid (GABA) and glutamate neurotransmitter systems that develop with sustained heavy alcohol use. Acamprosate is administered as 2 tablets 3 times daily or 1 tablet 3 times daily for a glomerular filtration rate of 30 to 50 mL/min/1.73 m^2. Acamprosate is safe for patients with Child-Pugh class A and B cirrhosis, but is contraindicated if the glomerular filtration rate is less than 30 mL/min/1.73 m^2. In a meta-analysis that included 20 double-blind RCTs (N = 6380) of at least 12 weeks' duration, the number needed to treat to prevent 1 person from returning to any drinking was 11 (95% CI, 1-32) with acamprosate vs placebo.[4] Another meta-analysis of 35 trials (N = 8951) of at least 4 weeks' duration demonstrated a significant reduction in heavy drinking, defined as at least 4 standard drinks (women) or 5 standard drinks (men) in 1 sitting, for acamprosate compared with placebo (RR, 0.78 [95% CI, 0.71-0.85]).[6] Diarrhea is the most frequently reported adverse effect of acamprosate (range, 3.0%-63.7% with acamprosate, 1.6%-64.9% with placebo).[4]

Disulfiram

FDA approved for AUD in 1951, disulfiram irreversibly blocks aldehyde dehydrogenase, an important enzyme in the metabolism of

Table. Comparison of Medications Used to Treat Alcohol Use Disorder

	Naltrexone (oral)	Naltrexone (injectable)	Acamprosate	Supervised disulfiram	Topiramate
Strength of evidence for efficacy (abstinence)	Moderate	Low (no effect)	Moderate	Strong[a]	Insufficient
Strength of evidence for efficacy (reduced drinking)	Moderate	Low	Moderate	Not applicable	Moderate
Dose/regimen	50-mg Tablet by mouth daily	380-mg Intramuscular injection monthly	Two 333-mg tablets by mouth 3 times daily	250-mg Tablet by mouth daily	25-mg Tablet by mouth twice daily, with uptitration to 100 mg twice daily over 6-8 wk
Adverse events/safety	Nausea, dizziness	Nausea, dizziness, injection site reaction	Diarrhea	Disulfiram-ethanol reaction, fatigue, nausea, rare hepatotoxicity	Cognitive dysfunction, paresthesia, taste disturbance
Treatment goals	Reduced drinking over abstinence	Reduced drinking over abstinence	Abstinence over reduced drinking	Abstinence	Reduced drinking

[a] Only open-label randomized clinical trials.

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alcohol. When patients consume alcohol while taking disulfiram, acetaldehyde rapidly accumulates, causing the disulfiram-ethanol reaction, characterized by nausea, vomiting, headache, flushing, and palpitations. Disulfiram is most effective when another person—typically a friend or family member—supervises adherence to daily dosing. Although disulfiram has been considered a second-line AUD medication in national guidelines,[2,3] newer analyses of prior data have shown greater efficacy for supervised disulfiram.[6,7] A network meta-analysis of 156 RCTs (N = 27 334) of medications for AUD, including 13 disulfiram studies, reported that relative to placebo, disulfiram was more effective in promoting abstinence (RR, 1.71 [95% CI, 1.39-2.10]) than acamprosate (RR, 1.33 [95% CI, 1.15-1.54]) and oral naltrexone (RR, 1.15 [95% CI, 1.01-1.32]).[6] Because disulfiram's efficacy depends on anticipation of negative physiologic effects, in double-blind studies, both the placebo and treatment groups are inclined to avoid alcohol, thereby potentially obscuring treatment effects. Meta-analyses, including well-designed, open-label RCTs, have consistently demonstrated supervised disulfiram's efficacy in promoting sustained abstinence, while those that exclude open-label RCTs yield contradictory results.[4,7] A meta-analysis of 17 open-label RCTs (N = 2204) with treatment durations of 8 to 52 weeks showed a large treatment effect with disulfiram vs controls, which included placebo and active controls, such as naltrexone and acamprosate, in promoting abstinence, particularly in the 13 studies with supervised medication adherence (Hedges *g*, 0.82 [95% CI, 0.59-1.05]).[7] Aside from the negative physiologic effects of consuming alcohol with disulfiram, the most frequent adverse effects are fatigue, nausea, and, rarely, severe hepatotoxicity (less than 1 per 30 000 individuals).[8] To avoid the disulfiram-ethanol reaction, patients should abstain from alcohol for at least 24 hours before starting disulfiram. Disulfiram should be avoided in patients with Child-Pugh class B and C cirrhosis but can be used with caution in patients with class A cirrhosis.

Topiramate

Although not FDA approved for AUD, the anticonvulsant topiramate can be used for treatment of AUD. Like acamprosate, topiramate is thought to modulate GABA and glutamate transmission. A 2023 meta-analysis of 8 double-blind RCTs (N = 1080) with treatment duration of at least 12 weeks reported a significant reduction in the absolute percentage of drinking days with topiramate compared with placebo (weighted mean difference, −7.2% [95% CI, −14.3% to −0.1%]) and a reduction in the average number of drinks per day (weighted mean difference, −2.0 [95% CI, −3.1 to −1.0]).[4] Topiramate requires slow upward titration to treatment doses (100 to 150 mg twice daily) over 6 to 8 weeks to prevent self-limited neurologic effects, such as paresthesia (0%-57.3% with topiramate, 1.9%-29.4% with placebo), dysgeusia (taste disorder; 15.1%-53.3% with topiramate, 4.8%-31.3% with placebo), and cognitive dysfunction (12.6%-23.9% with topiramate, 5.4%-11.3% with placebo). The need for slow titration and common cognitive effects often limit use of topiramate.

Practical Considerations

After treatment goals, defined by the patient as either abstinence or reduced drinking, have been achieved with medications for AUD, guidelines recommend an additional 6 to 12 months of pharmacotherapy.[3]

Although AUD medications can be safely initiated and maintained by primary care clinicians,[9] inpatient clinicians should also consider initiating medications for AUD. Hospitalizations for alcohol-related complications present an opportune moment to initiate pharmacotherapy because patients may be motivated to abstain from alcohol. In a retrospective cohort study of 6794 patients with alcohol-related hospitalizations, after propensity matching, initiation of any AUD pharmacotherapy on discharge was associated with a 42% decreased incidence of the primary outcome (all-cause mortality, emergency department visits, and hospital readmissions) within 30 days of discharge (incident rate ratio, 0.58 [95% CI, 0.45-0.76]; absolute risk difference, −0.18 [95% CI, −0.26 to −0.11]).[10]

Conclusions

AUD is a highly prevalent and undertreated condition in the US. Naltrexone, acamprosate, and disulfiram are FDA-approved medications that are effective and safe treatments for AUD and may be initiated in inpatient and primary care settings.

ARTICLE INFORMATION

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REFERENCES

1. Morford KL, Tetrault JM, O'Connor PG. Alcohol and cancer risk. *JAMA*. 2025;334(10):908-909. doi:10.1001/jama.2025.11229

2. Reus VI, Fochtmann LJ, Bukstein O, et al. The American Psychiatric Association practice guideline for the pharmacological treatment of patients with alcohol use disorder. *Am J Psychiatry*. 2018;175(1):86-90. doi:10.1176/appi.ajp.2017.1750101

3. Perry C, Liberto J, Milliken C, et al; VA/DoD Guideline Development Group. The management of substance use disorders. *Ann Intern Med*. 2022;175(5):720-731. doi:10.7326/M21-4011

4. McPheeters M, O'Connor EA, Riley S, et al. Pharmacotherapy for alcohol use disorder. *JAMA*. 2023;330(17):1653-1665. doi:10.1001/jama.2023.19761

5. Harris MTH, Weinstein ZM, Walley AY. Medications for opioid use disorder, opioid withdrawal, and opioid overdose. *JAMA*. 2026;335(11):986-998. doi:10.1001/jama.2025.26348

6. Bahji A, Bach P, Danilewitz M, et al. Pharmacotherapies for adults with alcohol use disorders. *J Addict Med*. 2022;16(6):630-638. doi:10.1097/ADM.0000000000000992

7. Skinner MD, Lahmek P, Pham H, Aubin HJ. Disulfiram efficacy in the treatment of alcohol dependence. *PLoS One*. 2014;9(2):e87366. doi:10.1371/journal.pone.0087366

8. Luo J, Zeng Y, Chen Z, et al. Safety assessment of disulfiram. *Front Psychiatry*. 2024;15:1498204. doi:10.3389/fpsyt.2024.1498204

9. Anton RF, O'Malley SS, Ciraulo DA, et al; COMBINE Study Research Group. Combined pharmacotherapies and behavioral interventions for alcohol dependence: the COMBINE study. *JAMA*. 2006;295(17):2003-2017. doi:10.1001/jama.295.17.2003

10. Bernstein EY, Baggett TP, Trivedi S, et al. Outcomes after initiation of medications for alcohol use disorder at hospital discharge. *JAMA Netw Open*. 2024;7(3):e243387. doi:10.1001/jamanetworkopen.2024.3387

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