



Indian Health Service
National Pharmacy and Therapeutics Committee
Formulary Brief: Alcohol Use Disorder
-February 2022-



Background:

The Indian Health Service (IHS) National Pharmacy and Therapeutics Committee (NPTC) reviewed Alcohol Use Disorder (AUD) maintenance treatment at the February 2022 meeting. The NPTC last reviewed the treatment of AUD in February 2015, at which time naltrexone was added. During this review, the utility of acamprosate and non-FDA approved medications such as topiramate, gabapentin, baclofen, and varenicline were evaluated. At the conclusion of the review, the NPTC made **no modifications to the National Core Formulary**.

Discussion:

Alcohol use disorder is common in the United States and affects American Indian/Alaska Native (AI/AN) people disproportionately. According to the 2018 National Survey on Drug Use and Health (NSDUH), 5.4% of adults in the US met the DSM-V criteria for AUD, 10.1% were AI/AN.¹ The NSDUH data from 2016 to 2019 shows that past year AUD among AI/AN increased for those aged 12-17 and aged 18-25, while those aged 26 and older showed decreasing rates of AUD.² Screening, Brief Intervention and Referral to Treatment, U.S. Preventative Services Task Force Grade B evidence supports the use of screening tests to assess for unhealthy alcohol use.³ Screening tools such as AUDIT-C is recommended for adults, MAST-G for geriatric, and CRAFFT for adolescent populations, respectively.³

Alcohol use disorder is characterized by loss of control over alcohol consumption, accompanied by changes in brain regions responsible for the execution of motivated behaviors. The FDA-approved medications for AUD, naltrexone and acamprosate as well as non-FDA approved medications such as topiramate, gabapentin and varenicline target areas in the reward pathway to attenuate the reward. Disulfiram works by irreversibly inhibiting the liver enzyme, aldehyde dehydrogenase; when alcohol is ingested, a build-up of acetaldehyde causes a dangerous aversive experience.⁴ Due to the requirement for complete abstinence when on disulfiram, it was not considered useful for patients who may relapse or who could accidentally ingest alcohol through common items such as cough syrup or certain fermented foods.

To facilitate therapeutic alliance, AUD treatment goals should take into account patient goals. Treatments for AUD are most effective when medications and behavioral treatments are combined, and may include traditional healing practices.³ When selecting medications for maintenance AUD therapy, clinicians should consider co-existing medical comorbidities and medications, frequency that the medication must be taken, prior experience with treatment, as well as psychiatric comorbidities and the need to treat co-occurring mood and substance use disorders.³

The COMBINE Study, which is the largest pharmacotherapy trial conducted for alcoholism in the US, evaluated the efficacy of naltrexone and acamprosate, both alone and in combination, in the context of medical management with and without Combined Behavioral Intervention (CBI).⁵ The study showed that CBI alone was ineffective against relapse, but when combined with naltrexone was shown to improve percentage of days abstinent. The addition of medical management to naltrexone and CBI enhanced positive outcomes. Acamprosate, however, was not shown to produce better outcomes than placebo, although notably the study utilized a dose of 3 grams (vs the usual 2-gram dose).

Despite naltrexone, both oral and intramuscular formulations, being widely considered as first-line therapy for AUD; acamprosate is also FDA-approved and is endorsed by the American Psychiatric Association (2018), the Department of Veteran Affairs/Department of Defense (2021), and the British Columbia Centre on Substance Abuse (2019). A Cochrane meta-analysis published in 2010 of 24 RCTs (n=6,915) was conducted to assess the efficacy of acamprosate versus placebo or other standard pharmacological AUD treatments to reduce return to drinking and improve cumulative abstinence.⁶ Acamprosate was shown to reduce the risk to return to drinking after detoxification by 86% (NNT=9; 95% CI 6.66 to 14.28). It also was shown to increase the cumulative duration of abstinence by 11 days compared to placebo [MD 10.9 (95% CI 5.08 to 16.81)].

A 2020 network meta-analysis of 64 RCTs evaluated two or more primary care interventions for continuous abstinence and all cause dropouts at least 12 weeks after the start of the intervention. The quality of evidence ranged from very low to moderate. Moderate quality evidence showed that drop-out rates were higher for acamprosate than placebo, OR 0.73 (95% CI 0.62 to 0.86) and that abstinence at 12 weeks was low; OR 1.92 (95% CI 1.52 to 2.42). The authors concluded that acamprosate intervention had moderate evidence suggesting it is better than placebo in supporting detoxified, alcohol dependent patients to maintain abstinence for up to 12 months in primary care setting.

A 2014 Cochrane meta-analysis of 25 RCTs (n=2641) examined whether anticonvulsants alone or in combination with other medications would lead to alcohol abstinence or reduction in consumption.⁸ Drop-out rates were greater with levetiracetam, RR 0.94 (95% CI 0.29 to 3.04), and topiramate, RR 0.91 (95% CI 0.65 to 1.28) versus placebo. In the five studies that evaluated topiramate (Baltieri 2008; Johnson 2003; Johnson 2007; Likhitsathian 2013; Rubio 2009), the mean difference was -0.44 (95% CI -0.69 to -0.20); this difference was statistically significant in favor of topiramate in decreasing heavy drinking. When studies with high risk of bias were excluded, four studies remained and the difference remained statistically significant. With regard to continuous abstinence, three studies (Johnson 2003; Johnson 2007; Rubio 2009) reported a mean difference of 15.51 (95% CI 4.55 to 26.47); this difference was statistically significant also in favor of topiramate. When studies with high risk of bias were excluded, two studies remained, however the difference was no longer statistically significant. The authors concluded that topiramate had evidence of efficacy despite insufficient evidence to support the effectiveness of anticonvulsants for the treatment of alcohol dependence.

A 2014 dose-ranging RCT (n=150) examined the effect of two doses of gabapentin (900mg or 1800mg vs. placebo) on rates of abstinence or reduction of heavy drinking days at 12 weeks; and weeks 13 and 25 post-treatment. Rate of sustained 12-week abstinence was greater with the 1800mg group, 17% (95% CI, 8.9-30%; NNT=8) compared to the 900mg group, 11.1% (95% CI, 5.2-22%) and placebo 4.1% (95% CI, 1.1-13.7%). Reduction in heavy drinking days was also greater with the 1800mg group, 44.7%, (95% CI 31.4-58.8%; NNT=5), compared to the 900mg group 29.6% (95% CI, 19.1-42.8%) and placebo 22.5% (95% CI, 13.6-37.2%). Adverse events did not differ among groups with side effects of fatigue (23%), insomnia (18%), and headache (14%). For subjects who completed the trial, rates of complete abstinence, drinks per week, and number of heavy drinking days per week were sustained at 24-week follow-up. Authors also noted that gabapentin appeared to have a dose-dependent effect on participants' subjective ratings of mood, insomnia, and craving symptoms.

Baclofen, FDA-approved as a muscle relaxant, is off-label for the treatment of AUD. Its primary mechanism of action for alcohol dependence is presumed to be the reduction of the reinforcing properties of alcohol by suppressing alcohol-stimulated dopamine release in the mesolimbic dopamine system.¹⁰ The agonistic effects of baclofen at the GABA-B receptors located in several brain areas including the mesolimbic circuit, and the ventral tegmental area, inhibit alcohol-induced firing of dopaminergic neurons and of the alcohol-stimulated dopamine release in the nucleus accumbens, resulting in the reduction of reinforcing properties of alcohol. According to UpToDate, its use is supported by data from and guidelines for patients with alcoholic liver disease. Baclofen has a short half-life of 3-4 hours so frequent dosing is required (3-4 times daily).

A 2018 Cochrane meta-analysis of 12 RCTs examined outcomes of achieving alcohol abstinence and/or reduction of consumption, as well as safety in adults who were given baclofen monotherapy or in combination with pharmacologic relapse prevention treatment compared to placebo or acamprosate for 4 to 12 weeks.¹⁰ There was no difference between baclofen, placebo or the two-treatment group in terms of relapse to any drinking at end of treatment or percentage of days abstinent, dropouts at end of treatment, dropouts due to adverse events, craving, and effect on anxiety, frequency of use (defined as % of heavy drinking at the end of treatment), or mean percentage of days abstinent. Compared to placebo, baclofen is associated with increased rates of side effects including vertigo, drowsiness, paresthesias, and muscle spasms or rigidity. Authors concluded that the evidence did not support use of baclofen as first-line treatment with AUD.

The mechanism action for varenicline is thought to be due to its effect on nicotinic acetylcholine receptors in the ventral tegmental area, which modifies dopamine release in the nucleus accumbens. A meta-analysis of 10 RCTs found no evidence that varenicline decreased percentage of heavy drinking days, the number of drinks consumed per drinking day, or increased number of days abstinent.¹¹ There was a reported decrease in alcohol craving, but overall, there was mixed evidence of efficacy shown in trials. In a 2014 randomized 2x2 medication designed study, authors reported that low dose naltrexone (25mg daily) plus varenicline may decrease cravings for cigarettes after drinking, but did appear to attenuate a cigarette and alcohol 'high'.¹² Notably, the study targeted a blood alcohol concentration (BAC) of 0.06% which is not indicative of drinking patterns in moderate to severe AUD.

Medication for treatment of AUD is not recommended for use in pregnancy.^{13,14} Combining psychosocial interventions with pharmacotherapy has been shown to be superior to pharmacotherapy alone.¹³ Continuation of pharmacological treatment started prior to pregnancy should be evaluated on a case-by-case basis.¹⁴ Breastfeeding is not recommended if there is continued alcohol use or pharmacological treatment for maintenance of alcohol abstinence. A 2010 Cochrane Review determined a need for studies examining maternal abstinence using pharmaceutical interventions.¹⁵

Aggressive treatment is favored in adolescents and young adults to prevent the risk and consequences of developing AUD as they age.¹⁶ Naltrexone was shown to reduce percent of drinking days with elevated BAC ≥ 0.08 g/dL and reduced number of drinks per drinking occasion when taken as a daily dose and 2 hours before drinking situations.¹⁷

Aim for age-specific interventions that minimize shame and target stage of life concerns, loneliness, and grief that may be contributing to alcohol use in the elderly.¹⁸ Naltrexone is the medication of choice as it has similar tolerability to younger patients. Avoid disulfiram due high incidence of medical comorbidity and cognitive issues that may decrease understanding of disulfiram-alcohol interaction. Utilize caution in use of gabapentin (BEER's list) in patients with CrCl <60mL/min.

Findings:

Moderate evidence shows that topiramate was associated with better efficacy than other anticonvulsants in reductions of heavy drinking days and reduction of percent drinking days, but its tolerability profile may limit its use as it must be titrated up slowly to effect. Gabapentin's dose-dependent effect on improving rate of sustained abstinence with NNT=8 and improving rate of no heavy drinking with NNT=5 is tempered by the lack of trials with large sample sizes. Due to inconsistent findings, there is lack of clear evidence regarding the effectiveness of baclofen for the treatment of AUD. Varenicline was not considered first-line due to lack of evidence showing efficacy. Lastly, acamprosate showed decreased relapse to alcohol when compared with placebo (NNT = 9); its role in AUD appears to be in preventing relapse in patients already abstinent from alcohol although it can be started while the patient is still drinking. Although favorable findings were reported with acamprosate treatment in AUD, its high daily pill burden, thrice-daily administration, and low overall Agency-wide utilization led the NPTC to make no modifications to the National Core Formulary.

If you have any questions regarding this document, please contact the NPTC at IHSNPTC1@ihs.gov. For more information about the NPTC, please visit the [NPTC website](#).

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