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ALCOHOL CLINICAL & EXPERIMENTAL RESEARCH ISBRA

CRITICAL REVIEW

Medications for treating alcohol use disorder: A narrative review

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Abstract

Chronic heavy alcohol use impacts all major neurotransmitter systems and is associated with multiple medical, psychiatric, and social problems. Available evidence-based medications to treat alcohol use disorder (AUD) are underutilized in clinical practice. These medications promote abstinence or reduce alcohol consumption, though there are questions regarding their optimal dosage, length of treatment, and utility in combination with one another. Pharmacogenetic approaches, which use a patient's genetic make-up to inform medication selection, have garnered great interest but have yet to yield results robust enough to incorporate them in routine clinical care. This narrative review summarizes the evidence both for medications approved by the Food and Drug Administration (disulfiram, oral naltrexone, acamprosate, and extended-release naltrexone) and those commonly used off-label (e.g., gabapentin, baclofen, and topiramate) for AUD treatment. We discuss these drugs' mechanisms of action, clinical use, pharmacogenetic findings, and treatment recommendations. We conclude that the most consistent evidence supporting the pharmacotherapy of AUD is for the opioid antagonists, naltrexone and nalmefene (which is not approved in the United States), and topiramate. These medications demonstrate consistent small or moderate effects in reducing the frequency of drinking and/or heavy drinking. Lastly, we make suggestions for research needed to refine and expand the current literature on effective pharmacotherapy for AUD.

KEYWORDS
alcohol use disorder, medication-assisted treatment, medications, pharmacotherapy

INTRODUCTION

Alcohol affects all major neurotransmitter systems and alters the absorption and metabolism of nutrients. Chronic heavy drinking can disrupt intermediary metabolism and produce deficiency states. It can also result in physiological dependence, with abrupt cessation causing the emergence of a constellation of withdrawal signs and symptoms (the alcohol withdrawal syndrome). Even in the absence of withdrawal, chronic heavy drinking is associated with a variety of psychiatric symptoms and disorders. Although pharmacotherapy can be efficacious in addressing some of these alcohol-related effects, we focus here only on medications that reduce drinking. In presenting findings on specific medications, we focus primarily on meta-analyses. In the absence of a meta-analysis, we present the results of individual efficacy studies.

GENERAL CONSIDERATIONS IN THE PHARMACOTHERAPY OF ALCOHOL USE DISORDER

The four medications approved by the U.S. Food and Drug Administration (FDA) for treating alcohol use disorder (AUD) are shown in Table 1, which summarizes their FDA-approved indications and dosage, clinical trials dosage, evidence of efficacy, and most common adverse effects. Table 2 provides similar information for

four medications that have been studied extensively and, though not FDA-approved, are used off-label for treating AUD. Despite the availability of three of four FDA-approved medications as generic drugs, pharmacotherapy is underutilized in treating AUD (Joudrey et al., 2019; Mark et al., 2009), with an estimated 1.6% of patients with the disorder nationally reporting receipt of an FDA-approved medication (Han et al., 2021).

This article updates previously published reviews (e.g., Knox et al., 2019; Kranzler & Soyka, 2018) and includes meta-analyses that either compare multiple medications (e.g., Jonas et al., 2014; Minozzi et al., 2018; Palpacuer et al., 2018) or focus on individual medications (e.g., Blodgett et al., 2014; Fluyau et al., 2023; Kranzler, Feinn, et al., 2019; Skinner et al., 2014). We limit the discussion to medications with multiple studies of their efficacy.

MEDICATIONS TO REDUCE OR STOP DRINKING

These medications include the alcohol-sensitizing agent disulfiram and those with direct effects on the neurotransmitter systems that underlie drinking behavior.

Disulfiram was the first FDA-approved drug for treating AUD. Its approval in 1949 preceded the FDA requirement that medications show significant superiority to placebo in RCTs. The drug inhibits the enzyme aldehyde dehydrogenase (ALDH), which metabolizes acetaldehyde, a toxic intermediary metabolite of alcohol, to acetate. A dose-dependent elevation of the plasma concentration of acetaldehyde causes the disulfiram-ethanol reaction (DER), an aversive constellation of signs and symptoms (e.g., warmness and flushing of the skin, increased heart rate, palpitations, decreased blood pressure, nausea, vomiting, shortness of breath, sweating, dizziness, and blurred vision). Less commonly, the DER includes confusion, marked tachycardia, hypotension, or bradycardia and, rarely, cardiovascular collapse, congestive heart failure, or seizures. The threat of experiencing a DER is thought to prevent patients from drinking.

The daily dosage of disulfiram used in the United States is 250–500 mg/day, though some patients require greater than 1 g/day to produce a DER (Brewer, 1984). Because disulfiram binds irreversibly to ALDH, renewed enzyme activity is dependent on the synthesis of new protein, which can take at least 2 weeks from the last dose of disulfiram, during which time the patient should continue to avoid alcohol.

The largest and most rigorous study of disulfiram was a one-year, multicenter trial in 605 male veterans with AUD (Fuller et al., 1986). Participants were randomly assigned to receive disulfiram 1 mg/day or 250 mg/day or an inactive placebo. Patients who received disulfiram were told they were given the drug and to avoid drinking because of the potential for a DER, but patients and staff were blinded to the dosage. All three groups showed a positive association between medication adherence and abstinence, despite no advantage of the 250-mg/day dosage over either of the other two groups. Among patients who relapsed, the group receiving disulfiram 250 mg/day reported significantly fewer drinking days than the other two groups. Despite this effect, because disulfiram can produce a DER with any drinking, it is not a good candidate for use in nonabstinent individuals or for harm reduction.

A meta-analysis of 22 studies of disulfiram (seven blinded and 15 open-label studies) for treating AUD (Skinner et al., 2014) used the primary outcome specific to each trial. It showed that although disulfiram had a higher success rate than the control condition, only open-label trials showed the drug to be significantly more efficacious than controls.

Pharmacogenetics of disulfiram: Two studies that examined genetic moderators of disulfiram showed that individuals carrying single nucleotide polymorphisms (SNPs) in the dopamine β-hydroxylase (*DBH*) gene and carriers of the null allele of *ALDH2*, which encodes ALDH, may experience better outcomes with disulfiram treatment (Arias et al., 2014; Yoshimura et al., 2014). These retrospective findings require prospective replication.

Clinical use of disulfiram: Specific behavioral interventions aimed at enhancing adherence with disulfiram include incentivizing medication ingestion, regular reminders, and behavioral training and social support to reinforce adherence (Allen & Litten, 1992). Another approach is to contract with the patient and a significant other to work together to ensure adherence (O'Farrell et al., 1995) or to ensure supervision of ingestion by an individual nominated by the patient Chick et al. (1992).

A clinician who is considering prescribing disulfiram to a patient with AUD should inform the patient fully of the drug's potential hazards, including the need to avoid alcohol in over-the-counter preparations, foods, and hand sanitizers and drugs that interact with disulfiram. Although rare, because fulminant hepatic failure has been reported to occur with disulfiram treatment liver function tests are recommended prior to treatment, monthly for the first 3 months, and then 2–4 times annually thereafter.

Drugs that directly reduce alcohol consumption

Many medications are thought to reduce drinking or promote abstinence by altering activity in one or more of the neurotransmitter systems underlying alcohol's reinforcing or discriminative stimulus effects. Notably, these systems interact to influence drinking behavior.

Opioid antagonists

Naltrexone is an antagonist of mu, kappa, and delta opioid receptors. It was approved by the FDA in 1984 as an oral formulation to treat opioid use disorder (OUD) and in 1994 to treat AUD. In 2006, an extended-release formulation of naltrexone (XR-NTX) was approved to treat AUD and in 2010 to treat OUD. Naltrexone is metabolized in the liver into 6β-naltrexol, with terminal half-lives of approximately 9 and 8 h, respectively (Wall et al., 1981). The FDA approval of oral

TABLE 1 Medications approved by the US Food and Drug Administration (FDA) for treating alcohol use disorder.

Medication	Disulfiram	Naltrexone	Extended-release naltrexone	Acamprosate
Indication	Management of selected chronic alcohol patients who want to remain in a state of enforced sobriety	Treatment of alcohol dependence	Treatment of alcohol dependence in outpatients who can abstain from alcohol	Maintenance of abstinence from alcohol in patients with alcohol dependence
FDA- Approved Dosage	250–500 mg/day	50 mg/day	380 mg intramuscularly/month	1998 mg/day
Dosage in clinical trials	125–500 mg/day	Initially 25–50 mg/day with increases to 50–100 mg/day	190 or 380 mg intramuscularly/month	1000–3000 mg/day
Efficacy	In meta-analysis (Skinner et al., 2014; $N = 22$ studies and 2414 subjects), open-label disulfiram treatment ($N = 15$ studies) showed a medium-to-large effect on sustained abstinence from alcohol compared with control conditions. Blinded trials ($N = 7$ studies) showed no effect of disulfiram. Large effect compared with control conditions when medication compliance was supervised ($N = 13$ studies), but nonsignificant in unsupervised studies ($N = 9$; Skinner et al., 2014)	Meta-analysis of placebo-controlled trials (Jonas et al., 2014; $N = 16$ studies and 2347 subjects) showed a small effect of naltrexone 50 mg/day on the risk of any drinking (number needed to treat [NNT] = 20) and a small effect on the risk of binge drinking [$N = 19$ studies and 2875 subjects (NNT = 12)	In the only published placebo-controlled trial of extended-release naltrexone (Garbutt et al., 2005), the median monthly number of binge drinking days declined from 19.3/month at baseline to 6.0/month in the placebo group, 4.5/month in the 190-mg group, and 3.1 in the 380-mg group.	Meta-analysis of placebo-controlled trials (Jonas et al., 2014; $N = 16$ studies and 4847 subjects) showed a small effect on reducing the risk of any drinking among abstinent subjects (NNT = 12), but no significant effect on the likelihood of binge drinking.
Most common adverse effects	Moderate or severe drowsiness is most common; severe adverse events, which include hepatitis, neuropathy, optic neuritis, psychosis, and confusional states, are rare (Chick, 1999)	Somnolence, nausea, vomiting, decreased appetite, abdominal pain, insomnia, and dizziness (Rösner, Hackl-Herrwerth, Leucht, Vecchi, et al., 2010)	Same adverse events as oral naltrexone plus injection site reactions (swelling, pain, and induration)	Diarrhea was common, but the only adverse event that was more common with acamprosate than placebo (Rösner, Hackl-Herrwerth, Leucht, Lehert, et al., 2010)
Clinical notes	Should only be used in patients who are aware of the potential for adverse effects and who have a goal of complete abstinence from alcohol	Can block the effects of opioid analgesics and precipitate withdrawal in a patient physically dependent on opioids	Can block the effects of opioid analgesics and precipitate withdrawal in a patient physically dependent on opioids	Not metabolized (renally excreted), so can be used in patients with hepatic disease

Abbreviations: NNT, number needed to treat; RCT, randomized clinical trial.

Source: Table adapted from Kranzler and Soyka (2018).

TABLE 2 Non-FDA-approved medications for treating alcohol use disorder.

Medication	Nalmefene (oral formulation)	Baclofen	Gabapentin	Topiramate
Indication(s)	European Union: Help reduce alcohol consumption in adults with alcohol dependence who consume =>60 g (~4 drinks) per day (men) or>40 g (~3 drinks/day; women).	To alleviate signs and symptoms of spasticity resulting from multiple sclerosis	Manage postherpetic neuralgia in adults and adjunctive therapy in treating partial seizures in patients aged 3 and older	Monotherapy for partial onset or primary generalized tonic–clonic seizures; adjunctive therapy for partial onset seizures or primary generalized tonic–clonic seizures and seizures associated with Lennox–Gastaut syndrome; migraine prophylaxis; weight loss and chronic weight management (combined with phentermine)
Dosage for AUD	Dosage approved in the European Union: 18 mg/day, as needed Dosage in clinical trials: 5–80 mg/day in a single or twice daily dose	Dosage in clinical trials: 30–180 mg/day in up to four divided doses	Dosage in clinical trials: 600–1800 mg/day in three divided doses	Dosage in clinical trials: 75–300 mg/day in two divided doses
Effects	Meta-analysis of five RCTs ($N=2567$ participants; Palpacuer et al., 2018) showed a small effect on binge drinking at both 6 months and 1 year of treatment. Nalmefene was associated with a reduction in total alcohol consumption by 20% at 6 months.	A Cochrane meta-analysis of 12 RCTs ($N=1128$ participants; Minozzi et al., 2018) showed no difference between baclofen and placebo for return to any drinking, percentage of days abstinent or percentage of heavy drinking days. In a second meta-analysis of 13 RCTs ($N=1492$ participants; Pierce et al., 2018), baclofen was associated with a small-to-moderate effect on both the time to first drinking lapse and a likelihood of abstinence during treatment. The drug effect was evident at a dosage of ≤60 mg/day, with no effect at a higher dosage.	Meta-analysis of seven RCTs ($N=751$ participants; Kranzler et al., 2019) showed that for all six outcome measures effect estimates favored gabapentin over placebo, though only percentage of heavy drinking days was significant.	In a meta-analysis of seven RCTs ($N=1125$), there were small-to-medium effects of topiramate on abstinent days (Hedges' $g=0.468$) and binge drinking days (Hedges' $g=0.406$).
Most common adverse effects	Nausea (22.1%), dizziness (18.2%), insomnia (13.4%), headache (12.3%), vomiting (8.7%), fatigue (8.3%), somnolence (5.2%) (van den Brink et al., 2015)	With low-dose treatment (30 mg/day): drowsiness (39.1%), dizziness (26.4%), headache (25.3%), confusion (23.0%), muscle stiffness (16.1%), excessive perspiration (14.9%), itching/pruritis (14.9%), abnormal muscle movements (13.8%), numbness (12.6%), slurred speech (10.3%) (Hauser et al., 2017)	Dizziness (19.1%), somnolence (14.1%), ataxia or gait disorder (14.0%), peripheral edema (6.6%) (Wiffen et al., 2017)	Paresthesia (50.8%), dysgeusia (23.0%), anorexia (19.7%), difficulty with concentration/attention (14.8%), nervousness (14.2%), dizziness (11.5%), pruritis (10.4%) (Johnson et al., 2007). Transient mental slowing and modest reductions in verbal fluency and working memory are generally dose related (Smith et al., 2016)
Clinical notes	Not approved in the United States for treating AUD	Approved in France for use in the management of alcohol dependence at a maximum recommended dosage of 80 mg/day	Additional studies needed to validate medication effects	To reduce risk/severity of adverse effects, begin treatment at 25–50 mg/day, with increases of 25–50 mg/day at weekly intervals to a maximum of 200 mg/day. Contraindicated in patients with a predisposition or history of metabolic acidosis, renal calculi, or angle-closure glaucoma.

Abbreviations: NNT, number needed to treat; RCT, randomized clinical trial.

Source: Table adapted from Kranzler and Soyka (2018).

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naltrexone for treating AUD was based on its efficacy in preventing relapse to heavy drinking in two 12-week, single-site, randomized controlled trials (RCTs; O'Malley et al., 1992; Volpicelli et al., 1992). Although the total number of subjects in the two initial published studies was 174, the analysis that led to the FDA approval of oral naltrexone included a total of 186 patients (https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/018932s017lbl.pdf).

Meta-analyses have consistently shown that naltrexone is superior to placebo in reducing the risk of heavy drinking (Jonas et al., 2014; Palpacuer et al., 2018; Rösner, Hackl-Herrwerth, Leucht, Vecchi, et al., 2010). The most comprehensive meta-analysis of naltrexone to date included 53 RCTs and 9140 participants (Jonas et al., 2014), which yielded a number needed to treat (NNT) to prevent a return to heavy drinking of 12. A systematic review of naltrexone treatment in women with AUD identified seven studies that met criteria for inclusion. Although no meta-analysis was conducted, the authors concluded that the limited evidence suggested that naltrexone, relative to placebo, may have a very modest effect in reducing drinking alcohol quantity and delaying the time to relapse, but not on drinking frequency (Canidate et al., 2017). A secondary analysis of the COMBINE trial showed similar efficacy rates for naltrexone among men and women (Greenfield et al., 2010).

Two approaches have been tested as alternatives to the daily use of oral naltrexone. First is targeted use, where patients are counseled to take the medication in anticipation of a high-risk drinking situation (Kranzler et al., 1997). An 8-week, 4-cell RCT compared the effects of naltrexone 50 mg with those of placebo and daily with targeted administration in 153 problem drinkers (Kranzler et al., 2003). In this study, naltrexone treatment was associated with a 19% greater reduction in the likelihood of heavy drinking than placebo. Patients in the targeted condition, irrespective of medication condition, had a nearly 14% lower likelihood of drinking on a particular day than those treated daily.

A subsequent 12-week study used a similar design in a sample of 163 heavy drinkers whose goal was to reduce their drinking (Kranzler et al., 2009). During Week 12 of treatment, males in the targeted naltrexone group drank significantly fewer drinks per day than those in the three other groups. Irrespective of gender, the targeted naltrexone group drank significantly fewer drinks per drinking day than the three other groups during Week 12.

In a double-blind RCT, 120 sexual and gender minority men with mild-to-moderate AUD and binge drinking received targeted naltrexone 50 mg or placebo for 12 weeks (Santos et al., 2022). In intention-to-treat analyses, the naltrexone group reported a nearly 25% lower risk of binge drinking days and 30% fewer drinks per month, with both effects persisting at 6-month post-treatment follow-up. However, the concentration of phosphatidylethanol (PEth), a sensitive and specific biological measure of alcohol consumption (Wurst et al., 2015), failed to validate the self-reported findings.

A second alternative to daily oral naltrexone for treating AUD is XR-NTX. In a pilot study ($N = 20$; Kranzler et al., 1998), participants who received a subcutaneous XR-NTX formulation reduced the frequency of heavy drinking more than the placebo group. The first of two XR-NTX formulations subsequently developed for intramuscular injection was evaluated in a 12-week RCT in 315 patients (Kranzler et al., 2004), where it significantly delayed the onset of any drinking following initial abstinence, increased the total number of days of abstinence, and doubled the likelihood of total abstinence. A second intramuscular XR-NTX formulation was studied in 627 individuals with AUD who were randomly assigned to receive six monthly injections of XR-NTX 380 mg, XR-NTX 190 mg, or matching placebo (Garbutt et al., 2005). Only the 380-mg group showed a significantly greater reduction in the rate of heavy drinking than placebo, and this formulation was approved by the FDA for treating AUD. In a secondary analysis of data from that pivotal study (O'Malley et al., 2007), participants with >4 days of voluntary abstinence before treatment initiation (~13% of the total sample) who received XR-NTX ($n = 28$) had significantly better outcomes on a variety of drinking measures and levels of the hepatic enzyme gamma-glutamyltransferase (GGT) than the placebo group ($n = 26$). Consistent with these findings, the package insert for Vivitrol calls for abstinence in an outpatient setting prior to initiating treatment.

A pilot study of 45 male inpatients with AUD is the only direct comparison of NTX formulations. Participants received either a 30-day prescription of oral naltrexone 50 mg or a single XR-NTX 380-mg intramuscular injection prior to discharge (Busch et al., 2017). Both groups showed a 13.6% increase in days with no binge drinking. Given the small sample sizes and short study duration, more definitive studies comparing the two formulations are needed.

Another approach to improving the response to naltrexone treatment is to combine it with other medications. In a 12-week RCT, 160 detoxified AUD patients received treatment with naltrexone, acamprosate, naltrexone plus acamprosate, or placebo (Kiefer et al., 2003). Although there was no significant difference in outcomes between naltrexone and acamprosate, the combined medication group had significantly better outcomes than the acamprosate group but not the naltrexone group. The COMBINE Study (Anton et al., 2006), the largest AUD pharmacotherapy trial to date ($N = 1383$ recently abstinent participants), compared 4 months of treatment with naltrexone, acamprosate, both medications, and placebo, combined with either medical management (MM) or intensive psychotherapy (Anton et al., 2006). The combination of naltrexone with MM, compared with MM alone, produced modest improvements in heavy drinking days and percent days abstinent. The efficacy of naltrexone was not enhanced by combining it with acamprosate or adding an intensive psychosocial intervention. In the sections below that cover gabapentin and varenicline, we describe studies combining those medications with naltrexone in treating AUD.

A key consideration in using naltrexone to treat AUD is the optimal treatment duration, which remains to be determined. Most naltrexone RCTs have been of 12 weeks duration or less. An exception to this is the VA Cooperative Study (Krystal et al., 2001), a large, multicenter RCT ($N = 627$), which compared 12-week and 52-week treatments. The study failed to show beneficial effects of naltrexone on any outcome measure at either timepoint. The pivotal study of

XR-NTX ($N = 624$) was 6 months in duration (Garbutt et al., 2005). It showed that the 380-mg dose was significantly better than placebo in reducing heavy drinking.

Follow-up studies of patients treated with naltrexone (Anton et al., 2000, 2006; O'Malley et al., 1996) show that, following the cessation of treatment, the relapse rate, number of drinking days, and number of heavy drinking days in the naltrexone group gradually increase. A post-treatment reduction in the beneficial effects of XR-NTX on drinking outcomes was also seen in a study of 308 individuals with AUD who were experiencing homelessness (Collins et al., 2021).

Pharmacogenetics of naltrexone: Pharmacogenetic studies of naltrexone have compared the drug's efficacy among carriers of the 118G allele of *OPRM1*, the gene encoding the mu-opioid receptor, with homozygotes for the more common A118 allele. The hypothesis underlying these studies is that changes in the receptor encoded by the variant allele affect the binding and/or efficacy of the opioid antagonist. In a secondary analysis of 141 European-ancestry (EA) participants from three 12-week RCTs of naltrexone (Oslin et al., 2003), naltrexone treatment among 118G-allele carriers was associated with lower rates of relapse to heavy drinking and a longer time to relapse than placebo. A similar moderating effect of the SNP was seen in a secondary analysis of the COMBINE study ($n = 604$ EA participants; Anton, Oroszi, et al., 2008). However, other studies (Arias et al., 2014; Gelernter et al., 2007), including two prospective trials (Oslin et al., 2015; Schacht et al., 2017) failed to support the moderating effect of the A118G SNP on naltrexone treatment response. A meta-analysis of the pharmacogenetic effect that included data from seven RCTs (Hartwell et al., 2020) failed to show a significant effect on any of the five outcome measures examined. Thus, this SNP does not appear to identify potential responders to naltrexone treatment of AUD.

In an analysis of three AUD treatment trials of naltrexone and acamprosate ($N = 1083$ EA individuals), a genome-wide association study (GWAS; Biernacka et al., 2021), 14 SNPs in the *BRE* gene predicted time to heavy drinking. In the naltrexone-only analyses, one SNP (rs12749274) was associated with time to heavy drinking. Larger GWAS studies of medication effects on drinking outcomes in AUD are needed to advance the pharmacogenetics of AUD treatment.

Clinical use of naltrexone: Naltrexone is useful in reducing heavy drinking when administered orally using daily or targeted administration or as an XR-NTX formulation. XR-NTX may be more efficacious in reducing heavy drinking if the patient is abstinent prior to the initiation of treatment. Although it appears that longer than 16 weeks of treatment with naltrexone is required to sustain treatment effects in AUD (Anton et al., 2006), further research is needed to ascertain the optimal treatment duration. Finally, combining naltrexone with other medications to treat AUD has not consistently demonstrated superiority over naltrexone alone, a possible exception to this being the combination of naltrexone with gabapentin (discussed below).

Nalmefene is approved in the European Union as an oral tablet administered on an as-needed basis to reduce heavy drinking. Nalmefene has been tested in the United States as an oral formulation for treating AUD, though it is not approved for that indication. In a pilot study, oral nalmefene 40 mg/day was superior to both 10 mg/day of the drug and placebo in preventing relapse to heavy drinking in 21 individuals with AUD (Mason et al., 1994). A subsequent RCT ($N = 105$) compared nalmefene 20 and 80 mg/day with placebo. In an analysis that compared the two nalmefene groups jointly with placebo, the active medication was significantly better in reducing heavy drinking than placebo (Mason et al., 1999). However, a subsequent 12-week, multisite RCT ($N = 270$) that compared placebo with 5, 20, and 40 mg of nalmefene daily for treating AUD (Anton et al., 2004) showed no between-group differences on any self-reported or biological measures of drinking.

Three European multicenter trials of nalmefene lasting either six or 12 months tested the medication on an as-needed basis (total $N = 1997$; Gual et al., 2013; Mann et al., 2013; van den Brink et al., 2014). Overall, nalmefene reduced heavy drinking days by 1.6–2.3 days per month and total daily drinking volume by 0.5–1 standard drink per day more than placebo. Nalmefene also significantly reduced alanine serum aminotransferase concentrations in all three studies and serum GGT concentrations in two of the studies. These findings were the basis for the European Medicines Agency's approval of nalmefene 18 mg on an as-needed basis (no more than once daily) to reduce heavy drinking in alcohol-dependent individuals.

Pharmacogenetics of Nalmefene: A pharmacogenetic analysis of a Finnish RCT in which 272 alcohol-dependent patients received as-needed treatment with 10–40 mg of nalmefene or placebo for 28 weeks (Karhuvaara et al., 2007), evaluated the effects of multiple opioid receptor gene SNPs on treatment response. Despite a significant effect of nalmefene on drinking outcomes in the overall study (Karhuvaara et al., 2007), there were no main or moderating effects of the genotypes on drinking outcomes (Arias et al., 2008).

Acamprosate

Acamprosate (calcium acetylhomotaurinate) is an amino acid derivative and a weak antagonist of NMDA receptors and inhibitor of the glutamate metabotropic glutamate 5 receptor (Blednov & Harris, 2008; Mann et al., 2008). The safety and efficacy of acamprosate have been studied most widely in Europe and three European studies served as the basis for the FDA's approval of the drug for clinical use in the United States.

A meta-analysis of 27 acamprosate studies in 7519 patients (Jonas et al., 2014) estimated that the NNT for acamprosate to prevent a return to any drinking was 12. Nonetheless, two large multicenter trials in the United States (Anton et al., 2006; Mason et al., 2006), a large European study (Mann et al., 2009), and a large Australian study (Morley et al., 2006) failed to detect beneficial effects of acamprosate in treating AUD. In a meta-analysis

of 22 studies of acamprosate treatment, men and women did not differ on any measure of efficacy, safety, or tolerability (Mason & Lehert, 2012). Despite its approval by the FDA for relapse prevention, there is mixed evidence of acamprosate's efficacy, suggesting that only subgroups of patients respond well to the medication. Thus, additional research is needed to identify the patient characteristics and therapeutic approaches that maximize the response to acamprosate.

Pharmacogenetics of acamprosate: Ooteman et al. (2009), in a preliminary study comparing the effects of 21 days of treatment with acamprosate or naltrexone on cue-induced craving, SNPs in *DRD2*, *GABRA6*, and *GABRB2* moderated the response to acamprosate. These results require replication in larger samples with a longer period of medication administration and additional measures of treatment response. Other studies have provided preliminary evidence of a moderating effect on acamprosate's efficacy by variation in three other genes. These include *GRIN2B*, which encodes a glutamatergic (NMDA) receptor subunit (Karpyak et al., 2014), and *GATA4* (Kiefer et al., 2011), which encodes a regulatory protein implicated in the pathophysiology of alcohol dependence. In addition, in the GWAS of AUD treatment outcomes (Biernacka et al., 2021), rs77583603 was associated with time to relapse in the acamprosate-treated group. These studies also require prospective replication.

Anticonvulsants

Although a 12-month RCT of carbamazepine ($N = 29$; Mueller et al., 1997) provided preliminary evidence of the drug's efficacy in treating AUD, there have been no subsequent carbamazepine studies for this indication. Similarly, despite a 12-week pilot RCT of divalproex in individuals with AUD ($N = 31$), in which the active medication group had a lower likelihood of relapse to heavy drinking than the placebo group (Brady et al., 2002), there have not been subsequent studies of the medication for other than alcohol withdrawal treatment. Other anticonvulsants that have been studied more extensively for treating AUD include topiramate and gabapentin and, to a lesser extent, zonisamide.

Topiramate: A meta-analysis of seven RCTs (comprising 1125 participants with AUD) showed that topiramate had significant, small-to-moderate beneficial effects on aggregate measures of abstinence and heavy drinking, and GGT concentrations (Blodgett et al., 2014). A recent Bayesian meta-analysis (Fluyau et al., 2023) included 13 placebo-controlled RCTs (comprising 1397 participants with AUD). It showed significant moderate-sized beneficial effects of topiramate on the likelihood of abstinence, the number of heavy drinking days, craving, and GGT concentration.

Although efficacious in reducing drinking and heavy drinking, topiramate treatment is associated with a variety of adverse events, though these are generally mild to moderate in severity. Fluyau et al. (2023) found that the likelihood of participants experiencing paresthesia, drowsiness, and memory impairment was significantly more common with topiramate than placebo. Uncommon visual adverse events (e.g., myopia, angle-closure glaucoma, and increased intraocular pressure) have also been reported to be associated with topiramate treatment and these require its discontinuation. To minimize topiramate's adverse effects, a slow titration to the maximal tolerated dosage (e.g., up to 300 mg/day over 6–8 weeks) is recommended.

Pharmacogenetics of topiramate: A SNP (rs2832407) in the gene encoding the kainate receptor GluK1 subunit, to which topiramate binds (Kranzler et al., 2009), initially showed a moderating effect on topiramate's reduction of alcohol consumption and in topiramate-related adverse effects (Kranzler et al., 2014; Ray et al., 2009). However, a prospective study (Kranzler, Morris, et al., 2021) when analyzed separately and combined with data from the initial trial (Kranzler, Hartwell, et al., 2021) failed to demonstrate a moderating effect of the SNP.

Zonisamide showed promise in the treatment of alcohol use disorder in a laboratory-based study following a single 100-mg dose (Sarid-Segal et al., 2009) and in a placebo-controlled (Arias et al., 2010) clinical trial, where the maximal dosage was 600 mg/day. A 12-week RCT (Knapp et al., 2015) compared the effects of placebo with zonisamide (400 mg/day), topiramate (300 mg/day), and levetiracetam (2000 mg/day). Treatment with zonisamide or topiramate was associated with significantly greater reductions in drinks per day, percent days drinking, and percent days heavy drinking than placebo treatment. Levetiracetam was associated only with a reduction in percent days heavy drinking. Topiramate was also associated with significantly greater reports of mental slowing than placebo during the last 2 weeks of treatment, while treatment with either topiramate or zonisamide was associated with modest reductions in verbal fluency and working memory.

Gabapentin is widely prescribed, including being used off-label to treat a variety of psychiatric symptoms (Goodman & Brett, 2017). A meta-analysis of seven RCTs estimated the effects of gabapentin at dosages that ranged from 600 to 3600 mg/day on six alcohol-related outcomes in 751 individuals with AUD (Kranzler, Feinn, et al., 2019). Although all effect estimates favored gabapentin over placebo, the only significant difference was a medium-to-large effect on the percentage of heavy drinking days. Another meta-analysis (Ahmed et al., 2019) of 10 gabapentin studies, which included alcohol withdrawal treatment trials, showed significant effects of the medication on craving and alcohol withdrawal, but only in the analysis of single-group effects rather than in comparison with placebo.

Anton et al. (2011) treated 150 individuals for 16 weeks with naltrexone only (50 mg/day), naltrexone (50 mg/day) plus gabapentin (up to 1200 mg/day) for the first 6 weeks, or double placebo. The naltrexone–gabapentin group showed a significantly longer time to first heavy drinking day, fewer heavy drinking days, and fewer drinks per drinking day than the other two groups, though the differences diminished over the last 10 weeks of the study. Participants with a history of alcohol withdrawal had better outcomes when treated with naltrexone–gabapentin. The same group (Anton et al., 2020) conducted a 16-week RCT of gabapentin (up to 1200 mg/day) in treatment-seeking individuals with AUD and recent alcohol

withdrawal. A significantly greater proportion of evaluable participants in the gabapentin arm (27%) than in the placebo arm (9%) had no heavy drinking days, an NNT of 5.4. A significantly greater proportion of the gabapentin group (18%) than the placebo group (4%) also reported total abstinence, an NNT of 6.2. These effects were driven by effects in the high-withdrawal-severity subgroup (heavy drinking days: NNT = 3.1; abstinence: NNT = 2.7). These two studies suggest that gabapentin is most useful for treating AUD in individuals with a history or current high level of withdrawal severity.

Although the tolerability of gabapentin in AUD trials has generally been good, dosages greater than 1800 mg/day are associated with dizziness, somnolence, ataxia or gait disorder, and peripheral edema (Wang & Zhu, 2017; Wiffen et al., 2017). Furthermore, it has been estimated that 1% of the U.S. general population misuses gabapentin for recreational purposes, self-medication, or intentional self-harm, either alone or in combination with other substances (including alcohol; Smith et al., 2016).

Other medications with evidence of efficacy in treating AUD

Baclofen is a $GABA_B$ agonist widely used as an antispasmodic. Over the past two decades, it has been evaluated as a treatment for AUD and in 2018 it was approved in France for treating AUD. However, meta-analyses of the drug's effects in treating AUD yielded different conclusions concerning its efficacy.

A Cochrane meta-analysis (Minozzi et al., 2018) of 12 RCTs of 10–150 mg/day of baclofen in 1128 participants with alcohol dependence. Analyses showed no difference between baclofen and placebo on the primary outcomes of return to any drinking, percentage of days abstinent, or percentage of heavy drinking days at the end of treatment. However, baclofen treatment was associated with more drinks/drinking day and greater depression severity than placebo. Other adverse events significantly more common with baclofen therapy included vertigo, somnolence/sedation, paresthesia, and muscle spasms/rigidity.

In contrast, a meta-analysis of 13 RCTs comprising 1492 individuals with AUD (Pierce et al., 2018) showed that baclofen was associated with significant, small-to-medium effects on the time to first lapse to drinking and likelihood of abstinence during treatment. There was a significant difference based on dosage, with studies of ≤60 mg/day of baclofen showing an association of the drug with a medium-sized effect on the time to a first lapse in drinking, while studies of >60 mg/day did not. Higher daily alcohol consumption at baseline was associated with a larger baclofen treatment effect.

A more recent RCT of baclofen in the United States randomized 120 participants with AUD to receive treatment with 30 mg/day, 90 mg/day, or placebo (Garbutt et al., 2021). Results showed that individuals who received the active medication had fewer heavy drinking days and more days abstinent than those in the placebo group, effects driven by the response in the 90- mg/day group. Moreover, the study showed a moderating effect of gender, such that men had a better treatment response when treated with baclofen 90 mg/day dosage while women had a significant effect at 30 mg/day.

Although the basis for the wide discrepancy among baclofen studies is unclear, the inconsistent findings argue against its use as a first-line treatment for AUD. If the drug is used to treat AUD at a dosage of ≥60 mg/day, careful monitoring is required given the risk of sedation at higher dosages (Reynaud et al., 2017), which can be particularly problematic in combination with alcohol.

Pharmacogenetics of baclofen: A secondary analysis of data from a subset of AUD participants ($n = 72$) who were randomly assigned to treatment with baclofen (30 or 75 mg/day) or placebo (Morley et al., 2018) examined the moderating effect of rs29220 in *GABBR1*, which encodes a subunit of the $GABA_B$ receptor. Treatment with baclofen in rs29220*C-allele homozygotes was associated with a longer time to relapse and greater proportion of abstinent days than in participants with one or two rs29220*G alleles or those treated with placebo. No significant moderating effects were found for SNPs in *GABBR1* or *GABBR2* (which encodes a second $GABA_B$ receptor subunit). The authors concluded that population differences in the frequency of the rs29220 allele may help to explain baclofen's lack of efficacy in some studies, though this hypothesis requires empirical validation.

Ondansetron, a serotonin-3 receptor antagonist, was shown by Johnson, Roache, et al. (2000) to reduce drinking only among individuals with early-onset alcohol dependence (before age 25). At a dosage of 4 μg/kg twice daily—substantially lower than the dosage used for its anti-emetic effects—ondansetron was significantly superior to placebo on the proportion of days abstinent and the intensity of alcohol intake. In contrast, in individuals with late-onset alcohol dependence the effects of ondansetron on drinking behavior were comparable to those of placebo.

A pilot clinical trial (Johnson, Ait-Daoud, & Prihoda, 2000) and an fMRI study (Myrick et al., 2008) have shown that ondansetron combined with naltrexone may provide additional benefits. These include decreases in drinks per drinking day, craving for alcohol, and alcohol-cue-induced activation of the ventral striatum. Adequately powered studies are needed to validate the use of this combination therapy.

Johnson et al. (2011) subsequently determined that ondansetron reduced drinking only in alcohol-dependent participants with the LL genotype of a polymorphism in *SLC6A4*, the gene encoding the serotonin transporter protein (5-HTTLPR). In addition, a SNP in the 3′ untranslated region (3′UTR) of *SLC6A4* interacted with the 5-HTTLPR polymorphism to moderate the response to ondansetron. Thus, the effect of ondansetron to reduce drinking was greatest in individuals with the LL genotype at 5-HTTLPR and the TT genotype of the 3′UTR SNP. Further analysis of this study's findings identified three additional variants in serotonin-3 receptor genes that moderated the ondansetron response (Johnson et al., 2013).

A 16-week RCT ($N = 95$ individuals with AUD, including 58 of European and 37 of African ancestry) sought to replicate and extend these findings (Seneviratne et al., 2022) by comparing low-dose

ondansetron (0.33 mg twice daily) or placebo. To assess pharmacogenetic effects, the sample was stratified into "responsive" and "non-responsive" genotype groups using population-specific variation at genes encoding the serotonin transporter and the serotonin-3A and serotonin-3B receptors. The study yielded no evidence that low-dose oral ondansetron is beneficial in the treatment of AUD, irrespective of genotype or population group, thus failing to confirm prior study findings. Of note, the study was underpowered to identify medication by genotype interactions and did not use the same genotype combinations previously shown to moderate the response to ondansetron (Johnson et al., 2011, 2013).

Aripiprazole is an atypical antipsychotic agent that acts as a partial agonist at dopamine-2 and serotonin-1A receptors. The administration of aripiprazole over a 6-day period reduced drinking by alcohol-dependent subjects both prior to and during a human laboratory session (Voronin et al., 2008). However, a 12-week, multisite RCT of aripiprazole (Anton, Kranzler, et al., 2008) showed no difference between treatment groups on the percentage of days abstinent, the percentage of subjects no drinking days, and the time to first drinking day, though the aripiprazole group reported fewer drinks per drinking day than the placebo group.

Varenicline, a partial nicotinic receptor agonist, is FDA-approved for treating tobacco use disorder. Although some studies have shown that it reduces drinking more than placebo in individuals with AUD (e.g., Litten et al., 2013), a meta-analysis of 10 studies ($N = 731$, 55.1% of whom were smokers; Gandhi et al., 2020) showed no significant differences on alcohol consumption measures between treatment groups. The only measure on which varenicline was superior to placebo was craving, where varenicline-treated participants showed a significantly greater reduction than those on placebo. A 12-week RCT conducted in 165 daily smokers who drank heavily compared the addition of naltrexone 50 mg/day or placebo to 2 mg/day of varenicline. Varenicline plus placebo was associated with a greater rate of smoking abstinence than varenicline plus naltrexone. Although the addition of naltrexone to varenicline was associated with a greater reduction in drinks/drinking day, the primary alcohol-related outcome measure, the effect did not reach significance (Ray et al., 2021). In a secondary analysis of the study by Litten et al. (2013), individuals with a low level of AUD severity had significantly greater reductions in heavy drinking days, drinks per day, and drinks per drinking day than those receiving placebo (Donato et al., 2021). A secondary analysis by Haeny et al. (2021) of two placebo-controlled varenicline studies (Litten et al., 2013; O'Malley et al., 2018) showed that participants in both studies reduced the number of drinks consumed irrespective of treatment condition or race (White or Black).

Anti-inflammatory drugs

Ibudilast is a well-tolerated anti-inflammatory drug that has been on the market for over 30 years in Japan where it is used to treat asthma and poststroke complications. Ibudilast inhibits pro-inflammatory cytokines and multiple cyclic phosphodiesterases (PDE). In a human laboratory and a short-term treatment trial (Grodin et al., 2021; Ray et al., 2017), ibudilast, at a maximum dosage of 100 mg/day, was associated with reductions in heavy drinking and alcohol cue reactivity. A six-week clinical trial that aims to replicate the effects on alcohol consumption is currently underway (NCT05414240). Apremilast, also a PDE inhibitor, a target dosage of 90 mg/day of apremilast, was recently shown to reduce the number of drinks/day and the proportion of heavy drinking days in an 11-day trial in non-treatment-seeking individuals with AUD (Grigsby et al., 2023).

Psychedelic drugs

Psychedelic drugs have also been studied as treatments for AUD. A meta-analysis of six RCTs of LSD for treating alcoholism included a total of 536 participants, nearly all inpatients (Krebs & Johansen, 2012). Participants were randomly assigned to receive either a single dose of LSD or ephedrine, amphetamine, low-dose LSD, or no medication. The primary outcome in these studies was alcohol misuse at follow-up one to 12 months after discharge from treatment. LSD-treated participants were nearly twice as likely as those in the comparator condition to show significant improvement, an effect that was consistent across the six studies, yielding an estimated NNT of 6. The drug was well tolerated, with a total of eight acute adverse events across the trials and no evidence of lasting harmful effects.

Recently, Bogenschutz et al. (2022) conducted an RCT of psilocybin in 93 participants with alcohol dependence, comparing it with diphenhydramine, a sedating antihistamine. Study medication was administered during two day-long sessions at Weeks 4 and 8, with all participants also receiving 12 weeks of manualized motivational and cognitive behavioral therapy. Both treatments were generally well tolerated. During follow-up, the psilocybin group reduced the number of heavy drinking days by more than double that in the control group, a medium effect and an estimated NNT of 4.5. In addition, the percentage of individuals with no heavy drinking days during treatment in the psilocybin group was three times that in the diphenhydramine-treated group and the number of alcohol-related adverse consequences was significantly lower in the active treatment group.

SUMMARY

A practice guideline published by the Department of Veterans Affairs/Department of Defense recommends topiramate, disulfiram, acamprosate, and naltrexone as first-line treatments for AUD. A practice guideline published by the American Psychiatric Association (APA; Reus et al., 2018) recommends offering the FDA-approved medications (disulfiram, naltrexone, and acamprosate) to patients with moderate-to-severe AUD and gabapentin or topiramate to patients who prefer either of these drugs or do not tolerate or have

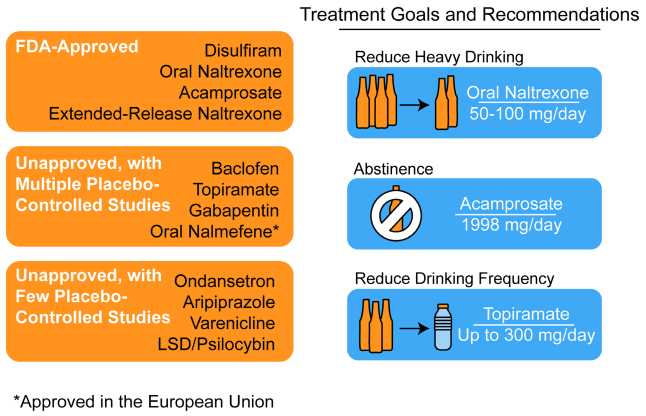

FIGURE 1 Medications for treating alcohol use disorder grouped by U.S. approval status and size of supporting literature.

not responded to the FDA-approved medications (Reus et al., 2018). Figure 1 provides a graphic summary of these findings.

The medications for which there is the most consistent evidence of efficacy in treating AUD are the opioid antagonists and topiramate. Opioid antagonists are associated with a small, but generally consistent, effect on reducing heavy drinking. Topiramate is associated with a small-to-medium effect on reducing the frequency of both any drinking and heavy drinking. The clinical utility of disulfiram seems to depend upon the availability of a mechanism to ensure adherence with the medication. Evidence supporting the use of acamprosate is consistent only for studies conducted in Europe, which show a small reduction in drinking frequency. In contrast, U.S. and Australian studies of acamprosate have not shown it to be efficacious. Although gabapentin showed a medium-to-large effect on reducing heavy drinking in a meta-analysis, the finding was driven largely by a single study. There are similar inconsistent findings with baclofen. Thus, we do not recommend gabapentin or baclofen as first-line treatments for AUD.

A systematic analysis of 28 studies that combined pharmacotherapy and cognitive behavioral therapy for AUD (van Amsterdam et al., 2022) showed that 10 of 19 RCTs (52.6%) showed that the combination was superior to psychotherapy alone, whereas only three of nine (33.3%) studies showed that combined therapy was superior to pharmacotherapy alone. The optimal approach to combining psychosocial and pharmacological treatments for specific patients remains to be determined (Ray et al., 2020). Further research is also needed to determine which patient groups, dosage schedules, and routes and durations of therapy are optimal when using the medications reviewed here.

Early findings that genetic variation moderates the response to naltrexone and topiramate have not been replicated and cannot be recommended at this time. Although a pharmacogenetic approach is one avenue by which the treatment of AUD could be enhanced, treatment response is a complex trait influenced by multiple genetic variants of small effect (Manolio et al., 2009). Thus, it is unlikely that a single SNP, even one that encodes an amino acid substitution, could be clinically useful in personalizing treatment. The use of polygenic risk scores (PRS, an overall measure of genetic risk for a trait) is more likely to provide clinically actionable predictors of treatment response. However, calculating PRS requires the availability of large GWAS of a trait in a discovery sample and genome-wide genotyping in a target sample (Wray et al., 2021). To date, the largest GWAS of an AUD pharmacotherapy sample that can be used as a discovery sample for calculating PRS (Biernacka et al., 2021) comprises only about 1000 EA individuals, a fraction of the number required to generate PRS powerful enough to predict treatment outcomes in an independent RCT.

CONCLUSIONS

Medications approved for treating AUD continue to be underutilized despite a near doubling in the last 20 years in the endorsement by addiction clinicians of the utility of naltrexone for treating AUD (Ehrie et al., 2020; Mark et al., 2003). Thus, additional efforts are needed to increase the appropriate prescribing of medications to optimize the care of patients with AUD, as pharmacotherapy should be a key element in efforts to reduce drinking or promote abstinence.

A key consideration in promoting effective pharmacotherapy is the development of data-driven guidelines on the optimal dosing and duration of treatment. There is also a need for well-powered studies of the safety and efficacy of medications in women, different groups based on ethnicity, race, sexual orientation, gender identity, as well as adolescent and geriatric populations. Studies of cost-effectiveness and cost-benefit are needed to support the routine coverage of pharmacotherapies for AUD by medical insurance plans. Finally, advances in the personalized treatment of AUD based on pharmacogenetics will depend on the availability of large datasets that include reliable measures of treatment outcome and a linkage to genome-wide genotype data.

To date, most studies of medications to treat AUD have focused on monotherapy. As the research literature on the use of medications to treat AUD grows, it will be possible to assess the utility of combining different medications with a variety of psychotherapies. There are ongoing efforts to personalize pharmacotherapy, based on clinical or genetic characteristics. With an increase in pharmacotherapeutic options, efforts should be directed to the alcohol treatment community writ large to promote their use as a standard ingredient in alcohol rehabilitation.

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CONFLICT OF INTEREST STATEMENT

Dr. Kranzler is a member of advisory boards for Dicerna Pharmaceuticals, Sophrosyne Pharmaceuticals, Enthion Pharmaceuticals, and Clearmind Medicine; a consultant to Sobrera Pharmaceuticals;

the recipient of research funding and medication supplies for an investigator-initiated study from Alkermes; a member of the American Society of Clinical Psychopharmacology's Alcohol Clinical Trials Initiative, which was supported in the last 3 years by Alkermes, Dicerna, Ethypharm, Lundbeck, Mitsubishi, and Otsuka; and a holder of U.S. patent 10,900,082 titled: "Genotype-guided dosing of opioid agonists," issued on January 26, 2021. Dr. Hartwell has no competing interests to declare.

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