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To cite this article: Raye Z. Litten Ph.D., Bonnie B. Wilford, Daniel E. Falk Ph.D., Megan L. Ryan & Joanne B. Fertig Ph.D. (2016): Potential Medications for the Treatment of Alcohol Use Disorder: An Evaluation of Clinical Efficacy and Safety, Substance Abuse, DOI: [10.1080/08897077.2015.1133472](https://doi.org/10.1080/08897077.2015.1133472)

To link to this article: <http://dx.doi.org/10.1080/08897077.2015.1133472>



Accepted author version posted online: 29 Feb 2016.



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Potential Medications for the Treatment of Alcohol Use Disorder: An Evaluation of Clinical Efficacy and Safety

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ABSTRACT

Alcohol use disorder (AUD), as currently defined in the *Diagnostic and Statistical Manual, Fifth Edition* (DSM--5), is a heterogeneous disorder stemming from a complex interaction of neurobiological, genetic, and environmental factors. As a result of this heterogeneity, there is no one treatment for AUD that will work for everyone. During the past two decades, efforts have been made to develop a menu of medications to give patients and clinicians more choices when seeking a therapy that is both effective and which has limited side effects. To date, three medications have been approved by the U.S. Food and Drug Administration (FDA) to treat alcohol dependence: disulfiram, naltrexone, and acamprosate. In addition to these approved medications, researchers have identified new therapeutic targets and, as a result, a number of alternative medications are now being evaluated for treatment of AUD in human studies. Although not approved by the FDA for the treatment of AUD, in some cases, these alternative

medications are being used off-label by clinicians for this purpose. These potential medications are reviewed here. They include nalmefene, varenicline, gabapentin, topiramate, zonisamide, baclofen, ondansetron, levetiracetam, quetiapine, aripiprazole, and serotonin reuptake inhibitors. The effectiveness of these medications has been mixed---some show good efficacy with side effects that are mild to moderate in intensity; others have mixed or promising results but are awaiting findings from ongoing studies; and still others show poor efficacy, despite promising preliminary results. Medications development remains a high priority. Key initiatives for the National Institute on Alcohol Abuse and Alcoholism (NIAAA) include supporting the discovery and development of more effective and safer medications, advancing the field of personalized medicine, and forging public and private partnerships to investigate new and more effective compounds.

Keywords

alcohol use disorder (AUD), medications development, personalized medicine, pharmacotherapy, novel medications

INTRODUCTION

Alcohol Use Disorder (AUD) is a devastating disease, resulting in a myriad of medical, psychological, social, and economic problems. Approximately 17 million Americans have a diagnosable AUD, causing 88,000 deaths annually and costing the United States (US) more than \$223.5 billion (<http://pubs.niaaa.nih.gov/publications/AlcoholFacts&Stats/AlcoholFacts&Stats.htm>). In the U.S. in 2005, AUD was responsible for 1.1 million life years lost from premature mortality, 2.4 million life years lost due to disability, and 3.6 million disability-adjusted life years lost.¹ Over the past two decades, advances have been made in developing pharmacological and behavioral interventions for alcohol dependence. Currently, three medications are approved by the US Food and Drug Administration (FDA) for the treatment of alcohol dependence---disulfiram, oral and extended-release injectable naltrexone, and acamprosate. These medications also are approved for use in Europe by the European Medications Agency (EMA), in Australia, and in a number of Asian countries. In addition to these medications, nalmefene has been approved in Europe, and baclofen has received a temporary recommendation for use in France. In general, the FDA and EMA have similar requirements for obtaining approval of medications to treat AUD. However, these two regulating agencies differ both in their primary endpoints and the length of trial required for regulatory approval. For instance, the FDA accepts only 6-month trials and uses total abstinence and no heavy drinking as endpoints, whereas the EMA recommends up to 15-month trials and uses endpoints related to reductions in drinking as well as total abstinence (<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm433618.pdf>;

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/03/WC500074898.pdf).

Despite their demonstrated efficacy, naltrexone, acamprosate, and disulfiram are not widely prescribed. Clinicians may not be aware of their usefulness, and consumers may not know they are available.^{2,3} To better inform clinicians and to raise public awareness, the Substance Abuse and Mental Health Services Administration (SAMHSA) and the National Institute on Alcohol Abuse and Alcoholism (NIAAA) have recently published practical guidelines for the use of FDA-approved AUD medications in clinical practice (<http://store.samhsa.gov/shin/content//SMA15-4907/SMA15-4907.pdf>).

A key barrier to the use of medications to treat AUD is the fact that, because of the heterogeneity of AUD, not all of these medications will be effective in every patient and in every circumstance.⁴ Instead, a menu of medications---each of which shows efficacy in certain groups of patients---might offer the best option. Clinicians then would have a wide variety of medications from which to choose and could target those drugs that are most effective to each individual patient---in short, personalizing medicine. Indeed, this is a treatment protocol that has proven especially effective in treating patients with depression, a similarly heterogeneous disorder.

This article summarizes potential medications for the treatment of AUD (Table 1). Medications include those approved by the FDA for use with other disorders that show efficacy for treating AUD, including nalmefene, varenicline, gabapentin, topiramate, and zonisamide; those with strong preliminary findings that are now being investigated in clinical trials, including baclofen and ondansetron; and those with promising preliminary results but poor efficacy in

recent clinical trials, including levetiracetam, quetiapine, aripiprazole, and serotonin reuptake inhibitors (SSRIs). This article, combined with the new SAMHSA/NIAAA guide to FDA-approved medications, should help clinicians better understand the medication options available to them. By knowing those options, clinicians can further personalize care for each individual patient and find the medication that is most effective and with the fewest side effects.

MEDICATIONS THAT EXHIBIT EFFICACY

Nalmefene

Nalmefene is an opioid antagonist that has been approved by the FDA for the treatment of opioid overdose. Although structurally similar to naltrexone, nalmefene has some key differences that may give it an advantage over naltrexone. It has a higher affinity to the opioid mu and kappa receptors, a higher bioavailability, and a lower risk for liver toxicity than naltrexone.^{5,6} The oral formulation of nalmefene (Selincro) recently was approved in Europe for the treatment of AUD. The oral formulation (Selincro) is not available in the U.S.; however, the liquid injectable form is available and is used to treat opioid overdose.

In a 12-week single-site randomized clinical trial (RCT) of 105 alcohol-dependent patients, Mason et al.⁷ first showed that nalmefene (20 mg/day and 80 mg/day) was more effective than a placebo in reducing relapse to heavy drinking, with both doses being equally effective. Thirty-seven percent of patients treated with nalmefene reported relapse to heavy drinking compared with 59 percent of patients treated with placebo. However, in a follow-up multisite US RCT of 270 alcohol-dependent patients, nalmefene (5 mg/day, 20 mg/day, and 40 mg/day) did not show any improvement over placebo in reducing the number of heavy drinking days or the time to first heavy drinking day.⁸ The lack of effect was attributed to variations in

study sites and the type of behavioral therapy used in the study (motivational enhancement therapy⁵ versus cognitive behavioral therapy in the Mason et al. study). In contrast, in Europe, three recent large multisite RCTs consistently showed a positive effect for nalmefene, which formed the basis for approval there. The first two trials (called ESENSE 1 and 2) included 604 and 718 alcohol-dependent patients at 39 and 57 sites, respectively.^{9,10} Nalmefene was taken as needed (one 18 mg tablet/day) if the patient perceived a risk of drinking alcohol. In ESENSE 1, the nalmefene group showed greater reductions in the number of heavy drinking days per month from baseline to the end of the 6-month treatment compared with the placebo group (19.4 to 8.2 vs. 19.6 to 10.7 heavy drinking days, respectively), as well as greater reductions in total alcohol consumption (84.0 to 33.3 g/day vs. 85.0 to 45.5 g/day, respectively). Results were comparable in ESENSE 2. The nalmefene group showed greater reductions in the number of heavy drinking days per month compared with the placebo group (19.8 to 6.6 vs. 18.3 to 7.5 heavy drinking days, respectively), as well as greater reductions in total alcohol consumption (93 to 30 g/day vs. 89 to 33 g/day, respectively). Pooling both studies demonstrated a significant effect for nalmefene in reducing the number of heavy drinking days and the total alcohol consumption.¹¹ A longer trial of 675 alcohol-dependent patients showed similar outcomes at month 13, although the differences were not significant at month 6.⁸ All three studies demonstrated that nalmefene was well tolerated, with the most common side effects (generally mild or moderate) being nausea, vomiting, fatigue, insomnia, and dizziness. Interestingly, all three studies found that patients with higher levels of alcohol consumption at the start of the study had a better response to the medication.^{11,12} To date, the manufacturer has not indicated plans to seek FDA approval for the use of nalmefene for the treatment of AUD in the U.S.

Summary for nalmefene:

- Efficacy: Good, according to recent European clinical trials.
- Side Effects: Nausea, vomiting, fatigue, insomnia, and dizziness.
- Market Availability: Approved in Europe for the treatment of alcohol dependence.
- Additional Comments: No plans indicated for FDA approval for the treatment of AUD.

Oral formulation is not available in the U.S.

Varenicline

Varenicline, a partial agonist at the $\alpha 4\beta 2$ receptor and full agonist at the $\alpha 7$ nicotinic acetylcholine receptor,¹³ has been approved by the FDA for smoking cessation. Recent evidence indicates that varenicline also reduces alcohol-drinking behavior. In several preclinical studies in animal models, varenicline was effective in reducing alcohol intake.¹⁴⁻⁻¹⁷ In a human laboratory paradigm, McKee et al.¹⁸ found that varenicline (at the same dose used for smoking cessation, 2 mg/day) was effective in reducing alcohol self-administration and craving in heavy drinkers who also were smokers. In addition, several small clinical trials showed that varenicline was effective in reducing drinking, heavy drinking and/or craving in heavy drinking smokers and alcohol-dependent patients.¹⁹⁻⁻²²

The most compelling evidence is from a recent multisite RCT of varenicline (2 mg/day) in 200 alcohol-dependent patients, approximately 40 percent of whom were smokers.²³ Compared with placebo, varenicline significantly reduced the primary outcome---percentage of heavy drinking days---by approximately 22 percent (37.9 percent for varenicline vs. 48.4 percent for placebo), as well as the number of drinks per day, drinks per drinking day, and alcohol craving. The efficacy was similar in both smokers and non-smokers. Varenicline also significantly reduced the number

of cigarettes per day, demonstrating that the medication reduces both drinking and smoking in this population. When moderator analyses were conducted, varenicline seemed to be more efficacious in reducing drinking in smokers who also reduced their smoking and in those with less severe alcohol dependence.²⁴ Varenicline was well tolerated. The most common adverse events (mostly mild) were nausea, abnormal dreams, and constipation. This study suggests that varenicline may be particularly useful with patients who would like to use a single medication to reduce their problem drinking and to also quit smoking.

The FDA issued a warning about possible neuropsychiatric side effects on mood, behavior, or thinking in some patients when taking varenicline. In addition, varenicline may change the way patients respond to alcohol, affecting their ability to tolerate its effects. Moreover, in rare accounts, seizures have been reported in patients taking varenicline. (See website for FDA warnings: [http://www.fda.gov/Drugs/DrugSafety/ucm436494.htm?source = govdelivery&utm_medium = email&utm_source = govdelivery](http://www.fda.gov/Drugs/DrugSafety/ucm436494.htm?source=govdelivery&utm_medium=email&utm_source=govdelivery).) These side effects were not seen in the multisite RCT; however, as part of the FDA's regulatory requirements, a Phase 4 clinical safety trial of varenicline is now being conducted by its manufacturer (Pfizer, Inc.) to further investigate its potential risks (projected completion date is late 2015). Pfizer has not indicated plans to advance this medication for the treatment of AUD.

Summary for varenicline:

- Efficacy: Good, especially for patients who wish to reduce drinking and stop smoking at the same time.
- Side Effects: Nausea, abnormal dreams, and constipation. FDA Box Warning: Patients should be observed for changes in behavior, hostility, agitation, depressed mood, and

suicide-related events. Although rare, seizures may occur. Finally, in some individuals, varenicline may affect their ability to tolerate alcohol.

- Market Availability: Available as an aid for smoking cessation.
- Additional Comments: Pfizer has not indicated plans to advance this medication for the treatment of AUD.

Gabapentin

Gabapentin is a medication approved by the FDA for the treatment of epileptic seizures, neuropathic pain, and restless legs syndrome. The exact mechanism of action is still unclear, but gabapentin appears to interact with the cell membrane's voltage-gated calcium channels to indirectly modulate GABA neurotransmission.²⁵ Evidence suggests that gabapentin is also a promising agent to treat alcohol dependence. Gabapentin has been shown to reduce the unpleasant symptoms of withdrawal that may lead to a relapse to drinking,²⁶ including helping to alleviate insomnia and craving.²⁷ Mason et al.²⁸ recently completed a 12-week trial of gabapentin (titrated to 900 mg/day and 1800 mg/day) with 150 alcohol-dependent patients. Compared with placebo, gabapentin (particularly the 1800-mg/day dosage) significantly improved the rates of abstinence and the number of patients who experienced no heavy drinking days. The abstinence rate was 17 percent in the 1800-mg group, 11 percent in the 900-mg group, and only 4.1 percent in the placebo group. The percentage of patients who did not engage in heavy drinking was 44.7 percent in the 1800-mg group, 29.6 percent in the 900-mg group, and 22.5 percent in the placebo group. Measures of mood, sleep, and craving also showed improvement. There were no serious adverse events. The most common side effects were mild and included fatigue, insomnia, and headaches. The dropout rate in this RCT was high (approximately 43percent), however, the

drinking outcomes of all subjects were sufficiently adjudicated as to preclude the need for any imputation of missing data.

Several small single-site RCTs also demonstrated that gabapentin is effective in reducing drinking. In a 6-week RCT, 21 patients with alcohol dependence and insomnia were given gabapentin (titrated to 1500 mg/day) and showed a delay in onset of heavy drinking, compared with controls. However, there was no benefit for insomnia.²⁹ In another RCT, 60 alcohol-dependent patients were administered gabapentin (600 mg/day) or placebo for 28 days.³⁰ The gabapentin group had fewer drinks per day, fewer heavy drinking days, and more days of abstinence compared with the placebo group. In yet another RCT, gabapentin (1200 mg/day) in combination with flumazenil was more effective than placebo in increasing the percent of days abstinent and time to first heavy drinking day in 16 alcohol-dependent patients with withdrawal symptoms.³¹ Finally, in a RCT in which gabapentin (titrated up to 1200 mg/day) was combined with naltrexone (50 mg/day), drinking outcomes improved, compared with the use of naltrexone alone.³²

NIAAA is currently conducting a multisite clinical trial of an extended-release form of gabapentin (Horizant) in AUD patients, in collaboration with the manufacturer (ClinicalTrials.gov: NCT02252536).

Summary for gabapentin:

- Efficacy: Good, particularly at higher dosage.
- Side Effects: Fatigue, insomnia, and headaches.
- Market Availability: Available for the treatment of epilepsy, neuropathic pain, and restless leg syndrome.

- Additional Comments: Gabapentin is not metabolized in the liver, allowing AUD patients with liver problems to take the medication. Results of an ongoing multisite trial may be used to apply for FDA approval for the treatment of AUD.

Topiramate

Topiramate is an anticonvulsant approved by the FDA for the treatment of seizures and migraines. In addition, topiramate, in combination with phentermine, has been approved for weight loss. It acts on numerous targets in the brain, facilitating GABA activity, antagonizing glutamate AMPA and kainate receptors, blocking L-type calcium channels, reducing voltage-dependent sodium channel activity, and inhibiting carbonic anhydrase.⁶ Topiramate is believed to affect drinking behavior by blunting alcohol-induced craving rather than by altering alcohol's stimulant or sedative effects.³³

In a single-site RCT of 150 alcohol-dependent patients, Johnson et al.³⁴ first demonstrated that topiramate (titrated to 300 mg/day), compared with placebo, was effective in reducing the number of drinks per day, the number of drinks per drinking days, and the number of heavy drinking days, while increasing the number of days abstinent. Side effects included dizziness, paresthesia, psychomotor slowing, memory or concentration impairment, and weight loss. These findings were reproduced in a 12-week multisite RCT of 371 alcohol-dependent patients.³⁵ Again, topiramate (titrated to 300 mg/day) reduced alcohol consumption and increased the number of days abstinent. Significant side effects included paresthesia, taste perversion, anorexia, insomnia, difficulty concentrating and paying attention, nervousness, and pruritus. In both studies, topiramate was slowly titrated (8 weeks in the single-site Johnson et al. study³⁴ and

6 weeks in the multisite Johnson et al. study³⁵), which is appropriate because slow-dose titration of topiramate has been associated with a lower rate of side effects.³⁶

More recent but much smaller studies support these earlier findings. In a 14-week clinical RCT, 21 alcohol-dependent patients who received topiramate (300 mg/day) experienced reductions in the number of drinks per day, number of drinks per drinking day, and percent of heavy drinking, as well as increases in the number of days abstinent compared with 24 patients receiving placebo.³⁷ However, patients treated with topiramate also experienced adverse cognitive side effects, including a significant increase on the mental-slowness subscale of the Neurotoxicity Scale and modest reductions in verbal fluency and working memory. In a 6-week clinical RCT of 52 alcohol-dependent patients, Martinotti et al.³⁸ reported that a low dose of topiramate (100 mg/day) was effective in reducing alcohol consumption, the frequency of drinking, and alcohol craving compared with the placebo group. The side-effect profile also appeared to be less significant than studies using 200 and 300 mg/day dosages. Finally, in a recent meta-analysis across 7 RCTs (total of 1,125 patients), topiramate was moderately beneficial for achieving abstinence and reducing heavy drinking.³⁹

Interestingly, a handful of recent studies indicate that topiramate may be even more efficacious in patients with certain genotypes and comorbid conditions. Kranzler et al.⁴⁰ conducted a 12-week RCT of topiramate (200 mg/day) in 138 alcohol-dependent patients. Topiramate significantly reduced the number of heavy drinking days and increased the number of days that patients remained abstinent, compared with a placebo. Moreover, patients who had a CC genotype (versus the AC and AA genotype) of the rs2832407 GRIK1 gene encoding the glutamate kainate GluK1 receptor not only had greater improvements in drinking outcome, but

this genotype also was the only one to show a treatment effect. Of note, even though the researchers administered a lower dose of topiramate, the side-effect profile was similar to the Johnson et al. study,³⁵ which used 300 mg/day. In another topiramate study,⁴¹ patients with the AA/AC genotype of the rs2832407 gene experienced more severe topiramate-induced side effects, compared with patients with the CC genotype. This suggests that patients with the CC genotype of the rs2832407 gene have a more efficacious response with fewer side effects. Finally, preliminary studies suggest that topiramate also may be effective in treating patients with comorbid disorders, such as AUD and post-traumatic stress disorder,⁴² and for treating patients addicted to cocaine with or without AUD.^{43,44}

Topiramate has gained acceptance with clinicians, especially those working within the US Department of Veterans Affairs. The number of topiramate prescriptions written for the treatment of AUD was second only to prescriptions for oral naltrexone.⁴⁵ Nevertheless, research continues to explore other medications that target similar sites in the brain with fewer side-effects (see zonisamide and levetiracetam below).

Summary for topiramate:

- Efficacy: Good.
- Side Effects: Dizziness, paresthesia, memory or concentration impairment, psychomotor slowing, nervous, taste perversion.
- Market Availability: Available for the treatment of seizures and migraines.
- Additional Comments: Recent preliminary studies suggest a favorable pharmacogenetic response to topiramate in terms of both efficacy and side effects. The pharmaceutical industry has not disclosed plans to advance this medication for the treatment of AUD.

Zonisamide

Zonisamide has been approved by the FDA as an adjunct treatment for partial seizures. This medication represents a new generation of anticonvulsants with multiple molecular actions in the brain. It enhances GABA function, blocks voltage-sensitive sodium channels and T-type calcium channels, and inhibits carbonic anhydrase.⁴⁶ The most common side effects of zonisamide are somnolence, anorexia, dizziness, headache, nausea, and agitation/irritability.⁴⁶ Like topiramate, zonisamide has been shown to decrease alcohol-drinking behavior but may also alter cognitive function (e.g., difficulty with memory and concentrating). Knapp et al.⁴⁷ reported that zonisamide decreased alcohol intake in rats and mice. In a human laboratory study, Sarid-Segal et al.⁴⁸ reported that zonisamide reduced both the urge to drink and the amount of alcohol consumed. In an open-label 13-week trial ($N = 16$), zonisamide (400 mg/day) reduced alcohol consumption in alcohol-dependent patients and was well-tolerated,⁴⁹ a finding replicated by another open-label trial ($N = 16$; 13 weeks), using 300 mg/day.⁵⁰ Arias et al.⁵¹ conducted a 12-week RCT of zonisamide (titrated to 500 mg/day) with 40 alcohol-dependent patients. Compared with placebo, zonisamide significantly reduced the number of heavy drinking days and number of drinks per week, as well as the urge to drink. Side effects generally were consistent with the label (all mild to moderate in severity), with the most common being gastrointestinal events. Knapp et al.³⁷ recently completed a 14-week RCT that measured the efficacy and safety of three anticonvulsants---zonisamide (400 mg/day), topiramate (300 mg/day), and levetiracetam (200 mg/day) in 85 alcohol-dependent patients. Compared with placebo, zonisamide and topiramate significantly reduced the number of drinks per day, number of days drinking, and number of heavy drinking days, whereas levetiracetam reduced only the number of heavy drinking days.

Topiramate also significantly reduced craving, whereas the zonisamide and levetiracetam results did not differ from the placebo. Both zonisamide and topiramate showed similar cognitive side effects, producing, on average, modest reductions in verbal fluency and working memory, although only the topiramate showed an average increase in mental slowing. Thus, preliminary evidence suggests that zonisamide may have similar efficacy as topiramate, with somewhat fewer side effects. Several ongoing trials of zonisamide are being conducted in alcohol-dependent patients with and without post-traumatic stress disorder (ClinicalTrials.gov NCT02368431 and NCT01847469).

Summary for zonisamide:

- Efficacy: Good.
- Side Effects: Similar to topiramate, although somewhat less severe.
- Market Availability: Available as an anticonvulsant. The pharmaceutical industry has not indicated plans to advance this medication for the treatment of AUD.

PROMISING MEDICATIONS THAT ARE AWAITING FINDINGS FROM ONGOING CLINICAL STUDIES

Baclofen

Baclofen is a GABA_B agonist that is FDA approved for the treatment of muscle spasticity. This medication has been shown to reduce alcohol intake in several animal studies⁶ and is thought to attenuate the symptoms of acute alcohol withdrawal in humans.^{52,53} RCTs have presented mixed evidence of efficacy in alcohol-dependent patients. A recent German RCT of 56 alcohol-dependent patients showed that a high dose of baclofen (titrated up to 270 mg/day) increased the rate of abstinence (68 percent in the baclofen group versus 24 percent in the

placebo group) and cumulative abstinence duration (68 percent in the baclofen group versus 52 percent in the placebo group) during the 12-week high-dose phase (240 to 280 mg/day) of the 20-week trial.⁵⁴ The medication was tolerated at this high dosage with few side effects. No significant differences were reported between the two groups, with fatigue and vertigo/dizziness approaching significance with baclofen. Using lower, more typical, doses of baclofen (30 mg/day), Addolorato et al.⁵⁵ also found a positive effect in a 1 month RCT of 39 alcohol-dependent patients. In that study, baclofen, compared with placebo, increased abstinence and reduced alcohol consumption and craving. The same researchers reproduced this finding in a larger 12-week RCT of baclofen (30 mg/day) in 84 alcohol-dependent patients with liver cirrhosis.⁵⁶ Patients given baclofen were twice as likely to maintain abstinence as those receiving the placebo, with no increase in hepatic side effects. The most common side effects were headaches, tiredness, vertigo, and sleepiness. In contrast, Garbutt et al.⁵⁷ conducted a 12-week RCT of baclofen (30 mg/day) in 80 alcohol-dependent patients and found no differences between the baclofen and the placebo groups in the number of heavy drinking days, number of days abstinent, time to first drink, time to relapse to heavy drinking, or craving. Interestingly, baclofen was associated with a reduction in state anxiety, consistent with its purported withdrawal-reducing effects. Baclofen was well tolerated. The most common side effects were drowsiness and headaches.

In another RCT, 42 alcohol-dependent patients received baclofen 30mg/day, baclofen 60 mg/day, or a placebo for 12 weeks.⁵⁸ There were no significant differences in drinking outcomes among the three groups; however, a secondary analysis indicated that baclofen (both doses) might be effective in altering drinking behavior in only a subgroup of patients (i.e., those with a

comorbid anxiety disorder). In a recent preliminary 12-week RCT of 30 alcohol-dependent smokers, baclofen (80 mg/day), compared with placebo, significantly reduced the number of days abstinent from the co-occurring use of alcohol and tobacco, but did not increase the number of days abstinent from alcohol alone.⁵⁹ Several large RCTs are being conducted in Europe. In particular, larger doses of baclofen (up to 300 mg/day) continue to be tested for both efficacy and safety. Currently, in France, baclofen was given a temporary recommendation for the treatment of alcohol dependence

(http://www.reddit.com/r/BaclofenForAlcoholism/comments/2ifiqx/baclofen_authorized_in_france_june_13_2014/).

Summary for baclofen:

- Efficacy: Mixed results from several clinical trials.
- Side Effects: Drowsiness and headaches.
- Market Availability: Approved for the treatment of muscle spasticity.
- Additional Comments: New clinical trials are being conducted at higher doses. Baclofen was given a temporary recommendation for the treatment of alcohol dependence in France.

Ondansetron

Ondansetron is a selective 5-HT₃ antagonist approved by the FDA for the treatment of nausea and vomiting. In a human laboratory study, Johnson et al.⁶⁰ found that ondansetron diminished the desire to drink and attenuated several of the pleasurable subjective effects of alcohol. In another human laboratory study, patients treated with ondansetron experienced an increase in both the stimulant and sedative effects of alcohol.⁶¹ In the first RCT, in 71 non-severe

alcohol-dependent patients, ondansetron reduced drinking from baseline to the end of treatment (35 percent reduction in the ondansetron group vs. 21 percent in the placebo group) in a subgroup of patients who already were drinking at relatively low levels (less than 10 drinks/drinking day).⁶² Johnson et al.⁶³ later conducted a larger 11-week RCT of ondansetron in 271 alcohol-dependent patients randomized to receive 2 µg/kg, 8 µg/kg, or 32 µg/kg per day of ondansetron or placebo. Patients were further randomized based on age onset of alcoholism (as determined by Item B28 of the Comprehensive Drinker Profile). Among those patients who developed alcoholism before age 25, ondansetron reduced the number of drinks per day and drinks per drinking day and increased the number of days abstinent as well as total abstinence, compared with placebo. The 8 µg/kg/day dose had greater efficacy than the other doses. Interestingly, this dosage was much lower than that used to treat nausea and vomiting (~0.8 mg/day for alcoholism versus at least 8 mg/day for nausea). Ondansetron had no effect on drinking outcomes in patients who developed alcoholism after age 25. No serious adverse effects occurred with ondansetron. The FDA has since issued a warning that ondansetron may increase the risk of developing abnormal changes in the electrical activity of the heart (QT interval prolongation) (<http://www.fda.gov/Drugs/DrugSafety/ucm271913.htm>). However, because low doses of ondansetron are showing promise in treating AUD, this side effect may not be significant.

Of particular note, a recent RCT by Johnson et al.⁶⁴ found that ondansetron was more efficacious than placebo in patients with a particular genetic polymorphism of the serotonin transporter (5-HTT) gene, which is believed to be associated with a wide range of psychiatric disorders.⁶⁴ Interestingly, Johnson and colleagues did not replicate their earlier finding that

patients with a younger age of onset of alcoholism showed better outcomes. In the RCT, 283 alcohol-dependent patients were randomized by genotype LL versus LS or SS of the serotonin transporter (5-HTT) and given 8 µg/kg/day of ondansetron or a placebo for 11 weeks. The SLC6A4 gene associated with 5-HTT⁶⁵ consists of two types of alleles, a long form (L) and a short form (S) with 44 less base pairs. Patients taking ondansetron who had the LL genotype (32 percent of the sample) had fewer drinks per drinking day and a higher number of days abstinent than those with the LS/SS genotype or patients with either genotype who were taking placebo. Johnson and colleagues also discovered a single-nucleotide polymorphism rs1042173 (T/G) in the 3'-untranslated region in SLC6A4. Approximately, one-third of the alcohol-dependent patients had the TT genotype whereas two-thirds had the TG/GG genotype. Interestingly, patients with the LL/TT genotype who received ondansetron had even fewer drinks per drinking day and a greater number of days abstinent than the other ondansetron allele and placebo groups. The most common side effects of ondansetron were insomnia, headache, appetite disturbance, fatigue, and diarrhea. In a later publication, Johnson and colleagues⁶⁶ found additional genetic polymorphisms in the 5-HT_{3A} and 5-HT_{3B} receptor subunits, including AC in the rs17614942 portion of the 5-HT_{3B} gene and AG in the rs1150226 and GG in the rs1176713 portion of the 5-HT gene. Ondansetron was most effective in reducing drinking in patients carrying one or more of these genetic variants. NIAAA is currently funding a two-site RCT of ondansetron to confirm these promising findings (ClinicalTrials.gov: NCT02354703).

Summary for ondansetron:

- Efficacy: Ondansetron appears to work in subgroups of patients with AUD. Preliminary results indicate that genetic polymorphisms of *5-HTT*, *5-HT_{3A}*, and *5-HT_{3B}* genes were associated with a response to ondansetron, although these findings need replication.
- Side Effects: Insomnia, headache, appetite disturbance, fatigue, and diarrhea. FDA Safety Precaution: Ondansetron can cause cardiac QT prolongation.
- Market Availability: Available for the treatment of nausea and vomiting.
- Additional Comments: An additional clinical trial is being conducted to confirm the pharmacogenetic findings of Johnson et al.^{65,66}

MEDICATIONS THAT HAVE SHOWN POOR EFFICACY DESPITE PROMISING PRELIMINARY STUDIES

Levetiracetam

Levetiracetam is another new anticonvulsant with a more modest side effect profile than both topiramate and zonisamide. It activates the GABA and glycine systems, inhibits AMPA receptors, depresses sodium-calcium channel current, and modulates the synaptic vesicle protein 2A.⁶⁷

Levetiracetam initially showed promise in reducing alcohol consumption in two open-label studies.^{68,69} It also appeared to have fewer cognitive side effects than topiramate.⁷⁰ However, more stringent RCTs have shown poor efficacy. For example, in a 16-week multisite RCT of levetiracetam (titrated to 2 g/day) with 130 alcohol-dependent patients, no differences were found between the levetiracetam and the placebo groups on any of the drinking outcomes.⁶⁷ The medication was well tolerated; compared with placebo, fatigue was the only significantly elevated adverse event. Levetiracetam was similarly ineffective at reducing drinking in two other

RCTs---a 16-week multisite RCT of 201 alcohol-dependent patients and a 6-week RCT of 46 non-treatment--seeking alcohol abusers.^{71,72} Finally, as previously indicated, Knapp et al.³⁷ conducted a trial comparing the efficacy and safety of zonisamide (400 mg/day), topiramate (300 mg/day), and levetiracetam (2 g/day) with placebo in 85 alcohol-dependent patients. Topiramate and zonisamide were more efficacious than levetiracetam in reducing drinking. Among all the drinking measures tested, levetiracetam significantly reduced only the number of heavy drinking days compared with the placebo. As expected, the safety profile of levetiracetam showed no cognitive impairment and thus was more favorable than that of topiramate and zonisamide. Importantly, these studies demonstrate that not all anticonvulsants are equally effective in reducing drinking.

Summary for levetiracetam:

- Efficacy: Poor.
- Side Effects: Fatigue.
- Market Availability: Available as an anticonvulsant.
- Additional Comments: Unlike other compounds in this class, such as topiramate and zonisamide, levetiracetam was not effective in treating AUD.

Quetiapine

Quetiapine is an atypical antipsychotic medication approved by the FDA to treat schizophrenia, manic episodes associated with bipolar I disorder, depressive episodes associated with bipolar disorder, and as an adjunct treatment for major depression (see FDA website: http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020639s049s054lbl.pdf). Quetiapine blocks multiple target receptors, including dopamine D₁ and D₂, serotonin (5-HT_{2A}), histamine

(H₁), and adrenergic (α_1 and α_2). Two human laboratory studies indicated that quetiapine (400 mg/day) reduced the craving and the sedative effects of alcohol, and improved subjects' ability to abstain from drinking.^{73,74} In addition, several preliminary open-label and retrospective studies indicated that quetiapine reduced alcohol consumption in alcohol-dependent patients.⁷⁵⁻⁷⁷ Kampman et al.⁷⁸ conducted a pilot 12-week RCT of quetiapine (400 mg/day) in 61 Type A and B alcohol-dependent patients. Type B alcoholics---characterized by an early age of onset of problem drinking, high severity of alcohol dependence, and increased psychopathology---experienced more days abstinent, fewer days of heavy drinking, and reduced craving with quetiapine than the placebo. In contrast, the Type A alcoholics---characterized by a late age of onset of problem drinking and low severity of alcohol dependence---did not benefit from quetiapine. To broaden these preliminary findings, a multisite 12-week RCT of quetiapine (titrated to 400 mg/day) was conducted in 224 alcohol-dependent patients.⁷⁹ No overall differences were detected between the quetiapine and placebo groups on a number of drinking measures. However, as expected, quetiapine significantly reduced depressive symptoms and improved sleep. In a subgroup analysis, the quetiapine and placebo groups did not differ significantly with regard to Type B status, sleep quality at baseline, presence of side effects, or quantity of medication taken during treatment. Quetiapine generally was well tolerated. The most common side effects were dizziness, dry mouth, dyspepsia, increased appetite, sedation, and somnolence. Finally, a 12-week RCT studied the effects of quetiapine (titrated up to 600 mg/day) in 90 alcohol-dependent patients with a co-occurring mental condition, including bipolar I or II disorders and depressed or mixed mood state.⁸⁰ Again, there were no differences in drinking outcomes between the quetiapine and placebo groups.

Summary for quetiapine:

- Efficacy: Although the preliminary results were promising, larger clinical trials showed no efficacy for treating AUD.
- Side Effects: Dizziness, dry mouth, dyspepsia, increased appetite, sedation, and somnolence. FDA Box Warning: Monitor patients closely for suicidal thoughts and behaviors.
- Market Availability: Available for the treatment of schizophrenia, manic episodes associated with bipolar I disorder, and depressive episodes associated with bipolar disorder.
- Additional Comments: The pharmaceutical industry has not indicated plans to advance this medication for the treatment of AUD.

Aripiprazole

Aripiprazole is another atypical antipsychotic medication approved by the FDA for the treatment of schizophrenia and bipolar disorder. It also is used as an adjunctive treatment for major depression (see FDA website:

http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/021436s028,021713s020,021729s013,021866s014lbl.pdf). It has multiple actions in the brain, including partial agonist activity at the D₂ and 5-HT_{1A} receptors and antagonist activity at the 5-HT_{2A} receptors.

Human laboratory studies suggest that aripiprazole may affect alcohol consumption and related outcomes. Kranzler et al.⁸¹ found that aripiprazole (2.5 mg/day and 10 mg/day) increased the sedative effects of alcohol and reduced the euphoric effects. In another laboratory study, aripiprazole (titrated up to 15 mg/day), compared with a placebo, reduced drinking in non-

treatment--seeking alcohol-dependent patients, but did not reduce the subjective “high” associated with drinking, degree of intoxication, or level of craving.⁸² Myrick et al.⁸³ reported that aripiprazole blunted the cue-induced brain activity in the ventral striatum, an area associated with the reinforcing aspects of alcohol. However, cue-induced craving for alcohol did not differ between the aripiprazole and placebo groups.

A 16-week RCT comparing aripiprazole (up to 15 mg/day) and naltrexone (50 mg/day) in 75 alcohol-dependent patients found that aripiprazole was as effective as naltrexone in increasing the number of days abstinent and reducing heavy drinking days.⁸⁴ However, in a multisite 12-week RCT of aripiprazole (titrated up to 30 mg/day) with 295 alcohol-dependent patients, no differences were found between the aripiprazole and the placebo groups in the number of days abstinent, number of subjects with no heavy drinking days, and time to first drinking day.⁸⁵ The authors postulated that the lack of efficacy may have been a result of dose-related attrition; that is, patients receiving aripiprazole had a higher dropout rate than those receiving placebo, primarily because of the side effects of the medication. The most common side effects from aripiprazole included fatigue, insomnia, restlessness, somnolence, anxiety, and disturbance in attention. Another human study with aripiprazole is ongoing (ClinicalTrials.gov: NCT01292057). Preliminary findings suggest that aripiprazole may be effective at lower doses (15 mg/day) and in alcohol-dependent patients who show a stronger tendency toward impulsivity.⁸⁶

Summary for aripiprazole:

- Efficacy: No efficacy was found in a large multisite clinical trial.

- Side Effects: Fatigue, insomnia, restlessness, somnolence, anxiety, and disturbance in attention. FDA Box Warning: Monitor patients closely for suicidal thoughts and behaviors.
- Market Availability: Available for the treatment of schizophrenia, bipolar disorder, and as an adjunctive treatment for major depression.
- Additional Comments: Currently a human study is being conducted to ascertain efficacy at lower doses and in subjects who are highly impulsive.

Serotonin Reuptake Inhibitors

Serotonin reuptake inhibitors (SSRIs) are approved by the FDA for the treatment of a variety of disorders, including depression and anxiety disorders.³ It should be noted that clinicians are more likely to prescribe antidepressants for patients with an alcohol dependence diagnosis than to prescribe those medications that currently are approved by the FDA for alcohol dependence⁸⁷ (MarketScan Commercial, 2010). In 2001, a survey of 1,388 physicians specializing in addiction medicine or addiction psychiatry (65 percent response rate) found that 46 percent prescribed antidepressants for alcoholism compared with 13 percent prescribing naltrexone and 9 percent disulfiram.⁸⁷ Although early animal models suggested that SSRIs were effective in reducing alcohol intake,³ most RCTs have ranged from no effect to only modest effects (reviewed by Johnson⁸⁸ and Litten et al.⁶). Of note, in a post-hoc analysis of an RCT, Kranzler et al.⁸⁹ found that Type B alcoholics (high-risk/severity, early onset of problem drinking) receiving fluoxetine experienced an increase in drinking compared with placebo, whereas Type A alcoholics (low-risk/severity, later onset of problem drinking) had the same results as the placebo group. A similar post-hoc analysis of another RCT (Pettinati et al.⁹⁰) found

that Type B alcoholics receiving sertraline had no change in drinking compared with placebo, whereas Type A alcoholics had a significant reduction in drinking compared with placebo. These analyses suggest that Type A alcoholics have a more favorable drinking outcome with SSRIs compared with Type B alcoholics. In addition, SSRIs may actually increase drinking in some Type B alcoholics.

Kranzler et al.⁹¹ followed up on these analyses by conducting a 12-week RCT of sertraline (200 mg/day) with 134 alcohol-dependent patients, looking in particular at the effects within subgroups of age of onset of alcoholism (a key criterion for the Type A/B distinction) and the LL/LS/SS polymorphisms of the SLC6A4 gene. Kranzler et al.⁹¹ employed a tri-allelic polymorphism grouping of the L allele. In this case, the L allele is defined not only by including the 44 base pairs (which are absent in the S allele), but also by including the A (versus G) single-nucleotide polymorphism in the L_A allele. This L_A allele is designated as L' by Kranzler et al.⁹¹ The L' allele is associated with greater mRNA concentrations, protein density, and 5-HT uptake activity than the low-activity S' allele (combined S and L_G alleles).⁹² In this study, among patients with the L'S'/S'S' genotype, sertraline was no more efficacious than placebo in reducing drinking regardless of age of onset of alcoholism. However, patients with the L'L' genotype and late onset of alcoholism (approximately 9 percent of patients with alcoholism) had fewer drinking days and fewer heavy drinking days than subjects receiving placebo. In contrast, patients with the L'L' genotype and early onset of alcoholism (approximately 16 percent of patients with alcoholism) experienced an increase in drinking days and in heavy drinking days compared with both the L'L' late onset of alcoholism group and the placebo group.

Overall, the efficacy of SSRIs in reducing drinking is modest at best,^{6,88} though there may be genetic subgroups that respond better to SSRIs. Nonetheless, evidence suggests that antidepressants reduce depressive symptoms to the same degree in depressed alcoholics as in depressed non-alcoholics.⁶ Thus, a combination of medications---one to treat the alcohol problem and another to treat the depression---may offer the best approach for this population.⁹³

Summary for SSRIs:

- Efficacy: Limited efficacy in the general AUD population, though genetic subgroups may respond better.
- Side Effects: Diarrhea, sexual problems, sleepiness/drowsiness, nausea, fatigue, and headaches. FDA Box Warning: Patients taking antidepressants should be monitored closely for suicidal thoughts and behaviors with antidepressants.
- Market Availability: Available for the treatment of a variety of mental health disorders, especially depression and anxiety disorders.
- Additional Comments: SSRIs can be used to treat depressive symptoms in depressed patients with AUD, although a small subset (early-onset of alcoholism, L/L ' genotype) could experience an increase in drinking.

FINAL COMMENTS AND CONCLUSIONS

As highlighted here, studies of potential medications for the treatment of AUD have yielded mixed findings. One group of medications (nalmefene, gabapentin, varenicline, topiramate, and zonisamide) show good efficacy, with side effects that were mild to moderate in intensity. A second group (baclofen, ondansetron) had mixed or promising preliminary results but is awaiting the findings of additional studies. A final group (levetiracetam, quetiapine, aripiprazole, and

SSRIs) had promising preliminary results but has not demonstrated efficacy in larger trials. Still, it is possible that the latter group may have a yet-to-be-discovered subset of patients who respond favorably to these medications.

To ensure continued momentum in advancing medications development, NIAAA has made this a key initiative, with a special focus on new types of compounds. More than 34 potential medication targets are now being explored for their potential usefulness in the treatment of AUD.⁹⁴ A number of NIAAA-supported human studies are in the early stages of development and are examining the following: pregabalin, oxytocin, duloxetine, doxazosin, olanzapine, mifepristone, oxcarbazepine, mirtazapine, guanfacine, dutasteride, fenofibrate, citicoline, mirtazapine, carisbamate, idazoxan, and prazosin. In addition, NIAAA recently issued a Funding Opportunity Announcement to evaluate promising medications in human studies (<http://grants.nih.gov/grants/guide/pa-files/PA-15-256.html>, <http://grants.nih.gov/grants/guide/pa-files/PA-15-254.html>, <http://grants.nih.gov/grants/guide/pa-files/PA-15-255.html>). This announcement is intended to foster the exploration of new targets and novel compounds as well as the repurposing of existing medications rather than further examining medications that already have been or currently are being evaluated, such as naltrexone, acamprosate, disulfiram, topiramate, ondansetron, varenicline, gabapentin, and baclofen.

The private sector also has shown increased interest in developing medications for AUD. Pharmaceutical firms recently supplied alcohol researchers with novel compounds that are being actively investigated in several NIAAA-supported human studies. These include compounds that

bind to corticotrophin-releasing factor (CRF), ghrelin, neurokinin, and vasopressin receptors, as well as an inhibitor of phosphodiesterase (see clinicaltrials.gov).

As noted earlier, part of the challenge in developing effective medications is dealing with the heterogeneous nature of AUD.⁴ As of now, there is no single treatment, either medication or behavioral therapy, that works for all patients. Therefore, the central goal is to provide clinicians with a menu of treatments from which to choose that will best meet the needs of each patient.

It also is important to provide clinicians with clear, concise guidelines that will enable them to administer medications in an effective, efficient, and safe manner. All medications have an individual risk-to-benefit ratio. Not only does the efficacy of a medication vary among AUD patients, but so does the side-effect profile. This scenario is not unlike the treatment of other complex medical disorders. For example, in treating major depression, patients often must try a variety of antidepressants before they experience relief from depressive symptoms and are able to tolerate the medication. In fact, a medication's side-effect profile is as important as its efficacy in deciding which medication to prescribe to the patient with major depression and to the patient with AUD.

Finally, the research summarized here shows clearly that there is no "silver bullet" medication for the treatment of AUD. The heterogeneity that makes up this disorder calls instead for a variety of medications that can be tailored to each individual. Understanding who will benefit the most from a particular medication is perhaps the most promising area of research for the medications development field. Advancing such personalized medicine will help take some of the guesswork out of prescribing medications, as compounds increasingly can be targeted to a

particular genetic makeup. This area is still in its very early stages, though progress is being made throughout the pharmacogenetic field.⁹⁵

To better understand the heterogeneity of AUD and who would benefit the most from a specific treatment, NIAAA is initiating a long-term research program to identify and measure different domains of alcohol addiction.⁴ Possible domains include reward, stress and affect regulation, incentive salience, executive function, and social processes.⁴ Developing ways to measure each domain and determining how a patient's vulnerability to AUD varies across those domains will be an important step forward in tailoring treatment to that individual's genetic and phenotypic profile. The challenge then will be to develop effective pharmacological and behavioral treatments that address the different domains of alcohol addiction.

In summary, significant advances have been made in medications development to treat AUD. In addition to the three medications already approved by the FDA, new medications are showing promise and many other medication targets are being explored. Over the next decade, the goal will be to develop a menu of effective and safe medications that will help improve treatment for this devastating disorder, offering relief for patients, their families, and overall public health.

ACKNOWLEDGEMENTS

The authors thank Barbara Vann of CSR, Incorporated, for her review and thoughtful comments. The views and opinions expressed in this paper are those of the authors and should not be construed to represent the views of the sponsoring agency or the Federal government. The authors declare that they have no conflicts of interest

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Table 1. Summary of Potential Medications to Treat AUD

Medication (Dose)	Site of Action	FDA Approval	Efficacy	Common Side-Effects	Next Step	Key References
Medications That Exhibit Efficacy						
Nalmefene (18 mg/day as needed)	Opioid antagonist	Reversal of opioid overdose; approved for alcohol dependence in Europe	Small effect in reducing drinking in three recent European trials	Nausea, vomiting, fatigue, insomnia, and dizziness	No plans for FDA approval for AUD	9--12
Varenicline (2 mg/day)	Partial $\alpha 4\beta 2$ and full $\alpha 7$ nicotinic agonist	Smoking cessation	Recent multisite RCT indicated that varenicline reduces drinking in alcohol-dependent smokers and non-smokers. Varenicline may be more effective in those who are less severely dependent and among smokers who also reduced their smoking.	Nausea, abnormal dreams, and constipation. FDA Box Warning includes hostility, agitation, depressed mood, and suicide-related events. Although rare, seizures may occur. In some individuals, varenicline may affect their ability to tolerate alcohol.	No plans for FDA approval for AUD	23,24
Gabapentin (900--)	Appears to	Adjunct treatment	Recent single-site	Fatigue, insomnia, and headaches	Ongoing multisite	28

1800 mg/day)	interact with voltage-gated calcium channels to indirectly modulate GABA activity	for partial seizure, neuropathic pain, restless legs syndrome	RCT demonstrated gabapentin is effective in increasing abstinence and number of no-heavy-drinking days		trial of gabapentin in U.S.	
Topiramate (200--300 mg/day)	Facilitates GABA activity, glutamate AMPA and kainate antagonist, blocks L-type calcium channels, reduces voltage-dependent sodium channel activity, inhibits carbonic anhydrase	Partial and tonic-clonic seizures, migraines. Combination of topiramate and phentermine as adjunct treatment for obesity.	Several RCTs, including one multisite study, have demonstrated efficacy in reducing alcohol consumption. Recent study indicated that genetic polymorphism in GRIK1 gene predicts a more favorable response to topiramate with fewer side effects.	Dizziness, paresthesia, memory or concentration impairment, psychomotor slowing, taste perversion, pruritus and weight loss	Ongoing multisite RCT to reproduce pharmacogenetic findings	34, 35, 40
Zonisamide (400--500	Enhances GABA activity,	Adjunct treatment for partial	Two single-site RCT trials	Side-effect profile is similar to topiramate,	Several ongoing trials	37, 51

mg/day)	blocks voltage-sensitive sodium channels, blocks T-type calcium channels, inhibits carbonic anhydrase	seizure	showed zonisamide was effective in reducing alcohol consumption. Zonisamide appears to exhibit efficacy similar to topiramate.	although somewhat less severe.		
Promising Medications That Are Awaiting Findings From Ongoing Clinical Studies						
Baclofen (30--80 mg/day) Higher doses are being explored	GABA _B agonist	Muscle spasticity	Several RCTs studies showed mixed results in reducing drinking.	Drowsiness and headaches	Several large ongoing studies, particularly testing higher doses for efficacy and safety	54, 56, 57
Ondansetron (8 µg/kg/day)	5-HT ₃ antagonist	Nausea and vomiting	Two large single-site RCTs demonstrated efficacy of ondansetron (low dose of 8 µg/kg/day) in reducing drinking, particularly	Insomnia, headache, appetite disturbance, fatigue, and diarrhea. There is an FDA safety precaution warning of a possible cardiac QT prolongation.	Ongoing multisite RCT to reproduce findings from previous single-site RCTs	63, 64, 66

			<p>in a subgroup of alcohol-dependent patients. The first RCT showed that patients with early-onset of alcoholism (25 years or younger) responded to ondansetron treatment. The second RCT did not replicate this finding, but did show that genetic polymorphisms of 5-HTT, 5-HT_{3A}, and 5-HT_{3B} genes were associated with a greater response to ondansetron.</p>			
Medications That Have Shown Poor Efficacy Despite Promising Preliminary Studies						
Levetiracetam (2	Activates GABA	Adjunct treatment	Two multisite	Fatigue. Fewer side effects than	None; it appears	37, 67, 71

gm/day)	and glycine systems , inhibits glutamate AMPA, depresses sodium-calcium channel current, modulates synaptic vesicle protein 2A	for myoclonic seizure, partial seizure, tonic-clonic seizure	RCTs trials showed no effect in reducing drinking.	the anticonvulsants topiramate and zonisamide.	to have no effect in treating AUD.	
Quetiapine (400 mg/day)	Blocks dopamine D ₁ and D ₂ , 5-HT _{2A} , histamine H ₁ , and adrenergic α_1 and α_2	Schizophrenia, manic episodes associated with bipolar I disorder, depressive episodes associated with bipolar disorder, adjunct treatment for major depressive disorder	Despite promising results in preliminary human studies, quetiapine was not effective in a multisite and single-site RCT. In the multisite RCT, no promising subgroups of patients could be identified.	Dizziness, dry mouth, dyspepsia, increased appetite, sedation, and somnolence. FDA Box Warning for suicidal thoughts and behaviors.	None; it appears to have no effect in treating AUD.	79, 80
Aripiprazole (15--30 mg/day)	Partial agonist at D ₂	Schizophrenia, bipolar disorder,	Small human studies	Fatigue, insomnia, restlessness, somnolence,	Addition al human	85

	and 5-HT _{1A} receptors, 5-HT _{2A} antagonist	adjunct treatment for major depression	suggested efficacy for reducing drinking. However, a multisite RCT showed no efficacy at a 30mg/day dose.	anxiety, and disturbance in attention. FDA Box Warning for suicidal thoughts and behaviors.	studies are ongoing at lower doses (15 mg/day)	
Serotonin reuptake inhibitors (SSRIs) (Doses vary with type of SSRI)	Serotonin reuptake inhibitor	Major depressive disorder, obsessive-compulsive disorder, panic disorder, posttraumatic stress disorder, premenstrual dysphoric disorder, social phobia, bulimia nervosa	Despite being prescribed by many clinicians for AUD, most RCTs range from no effect to modest effect in reducing drinking. Post-hoc analysis indicates that Type A alcoholics respond better to SSRIs than Type B alcoholics. Recent RCT study indicates that response may dependent on age of onset of	Diarrhea, sexual problems, sleepiness/drowsiness, nausea, fatigue, and headache. FDA Box Warning for suicidal thoughts and behaviors.	SSRIs can be used to treat depression in depressed AUD patients, although a small subset could experience an increase in drinking.	6, 88, 91

			alcoholism and polymorphi sm of the 5- <i>HTT</i> gene.			
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