HHS Public Access

Author manuscript

Harv Rev Psychiatry. Author manuscript; available in PMC 2016 March 14.

Published in final edited form as:

Harv Rev Psychiatry. 2015 ; 23(2): 122–133. doi:10.1097/HRP.0000000000000079.

Pharmacotherapy for Alcohol Use Disorder: Current and Emerging Therapies

Dr. Robert M. Swift, MD, PhD and **Dr. Elizabeth R. Aston, PhD**

Department of Psychiatry and Human Behavior, Brown University Alpert School of Medicine (Dr. Swift); Center for Alcohol and Addiction Studies, Brown University School of Public Health (Drs. Swift and Aston); VA Medical Center, Providence, RI (Dr. Swift)

Abstract

Alcohol use disorder is a heterogeneous illness with a complex biology that is controlled by many genes and gene-by-environment interactions. Several efficacious, evidence-based treatments currently exist for treating and managing alcohol use disorder, including a number of pharmacotherapies that target specific aspects of biology that initiate and maintain dangerous alcohol misuse. This article reviews the neurobiological and neurobehavioral foundation of alcohol use disorder, the mechanisms of action and evidence for the efficacy of currently approved medications for treatment, and the literature on other emerging pharmacotherapies.

Keywords

alcohol dependence; alcohol use disorder; pharmacotherapy

Alcohol use disorder (AUD),[1] called alcohol dependence in DSM-IV[2] and commonly referred to as “alcoholism,” is a significant medical and social problem in American society, accounting for 88,000 excess deaths per year and more than $250 billion in annual costs.[3,4] Fortunately, the personal and societal impact of AUD can be reduced through treatment, which consists of psychological, social, and pharmaceutical interventions to reduce alcohol consumption and its consequences.[5] While a number of successful, evidence-based treatments for AUD currently exist, treatment is not successful for all patients.[6] Moreover, epidemiological research indicates that most persons with AUD are currently neither under nor seeking treatment.[7] Thus, improving existing treatment and access to treatment are major priorities.

The main goal of AUD treatment is to help patients avoid alcohol entirely (abstinence) or to reduce alcohol drinking (harm reduction). While it remains controversial whether abstinence or reduced drinking should be the preferred goal of treatment, both approaches have benefits. Research indicates that abstinence has the best outcome, but significant

Correspondence: Robert M. Swift, MD, PhD, ACOS for Education, VA Medical Center, 830 Chalkstone Ave., Providence, RI 02908. robert_swift_md@brown.edu.

Declaration of interest: Dr. Swift is a member of an advisory board for D&A Pharma and has received honoraria and travel reimbursements from the company. He has received research funding, consulting fees, and travel reimbursement from Farmaceutico CT, and honoraria and travel reimbursements from Lundbeck.

improvements in health and quality of life can occur with reductions in drinking.[8] In the United States, evidence-based psychosocial treatments (e.g., motivational enhancement therapy, cognitive-behavioral therapy, brief interventions, Alcoholics Anonymous) are the most commonly available treatment modalities for AUD,[9] and pharmacotherapies are less commonly available. Psychosocial treatments aim to develop cognitive skills to avoid drinking or manage drinking situations, address psychological issues that promote drinking, provide social support, and improve self-esteem and self-efficacy.

Over the past 25 years, emerging knowledge about the brain has improved our understanding of how alcohol acts on neural circuits and leads to the development of AUD in conjunction with psychological and social factors.[10] Developing over time, AUD can both result in, and be the result of, alcohol-induced changes in the structure and function of certain neural circuits.[11] Moreover, it is a likely that a robust genetic influence predisposes certain individuals to develop AUD. The improved knowledge of AUD's biological basis has led to the development of several biologically based pharmacotherapies to treat the disorder. The US Food and Drug Administration (FDA) has currently approved four medications for treating AUD—namely, disulfiram, oral naltrexone, extended-release injectable naltrexone, and acamprosate.[12] Two other medications, gamma-hydroxybutyrate and nalmefene, have been approved by the European Medications Agency for use in Europe.[13] A number of other pharmacotherapies have not been approved by regulatory agencies but are used off-label to treat AUD. Still others are under development.

Pharmacotherapies can complement psychosocial treatment by countering one or more of the neurobehavioral mechanisms that initiate and maintain alcohol use. For example, medications such as disulfiram and opioid antagonists counter the positively reinforcing stimulant effects of alcohol and increase its aversive effects. Disulfiram alters alcohol metabolism, and opioid antagonists block alcohol-induced release of endorphins. Disulfiram and opioid antagonists may also reduce the craving or urge for alcohol. Some pharmacotherapies partially substitute for alcohol to maintain the neurobehavioral effects of alcohol but without its deleterious effects.[14] Antiepileptic medications such as topiramate and gabapentin partially substitute for alcohol at glutamate receptors, γ-aminobutyric acid (GABA) receptors, and other ion channels, thereby attenuating or preventing symptoms, alcohol withdrawal, and allostasis. Thus, by acting on physiological and neurobehavioral systems that mediate AUD, medications can either decrease the likelihood of relapse in those who are abstinent or, instead, reduce the quantity and frequency of alcohol consumed.

METHODS

This review discusses the neurobiological and neurobehavioral basis of AUD, the mechanisms of action of various pharmacotherapies that are intended to treat AUD, and the evidence for the efficacy of such pharmacotherapies. This review describes approved, off-label, and novel pharmacotherapies for treating AUD. As such, specific articles were selected to display the range of findings for each currently accepted and potentially effective pharmacotherapy. The articles used in the discussion of medication efficacy were restricted to double-blind, placebo-controlled clinical trials and meta-analyses.

THE NEUROBIOLOGY OF AUD

The development of AUD is a complex process involving interactions among neurobehavioral systems that promote or inhibit the consumption of alcohol. Alcohol consumption is promoted through the activation of neural circuits that produce stimulation and positive mood responses (reward) and that relieve stress and negative moods (relief). The rewarding effects of alcohol occur through the activation of mesolimbic circuits—the same system that regulates responses to natural reinforcers such as food, sex, and social interactions.[15] Rewarding stimuli release the neurotransmitter dopamine into the nucleus accumbens, amygdala, and prefrontal cortex, resulting in increased salience of the stimulus, increased attention to the stimulus, and increased wanting or desire for it.[16]

At the same time, alcohol produces unpleasant effects—such as sedation, negative moods, and motor impairments—that typically deter alcohol consumption.[17] The sedation results from enhanced inhibitory GABA neurotransmission via alcohol's direct action on GABA-A receptors. Alcohol reduces excitatory glutamatergic neurotransmission by attenuating excitatory glutamate responses at N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptors. Alcohol also releases dynorphins, which produce negative mood effects and cognitive dysfunction.

Alcohol consumption is influenced by general appetitive mechanisms in the hypothalamus and other brain areas that control food consumption by moderating appetite and satiety. Appetite and weight are controlled by a complex system involving multiple neurotransmitters and circuits. Hypothalamic homeostatic signals that are mediated by agouti-related peptide, calcitonin gene-related peptide, proopiomelanocortin, and neuropeptide Yare integrated with reward circuitry, stress response circuitry, and peripheral hormone signals from the gut and adipose tissue.[18] Increasing the gain in this system increases consummatory behaviors. Neurotransmitters and hormones that increase appetite and food consumption, such as opioids or the stomach hormone ghrelin, are associated with increased alcohol consumption.

Individuals with certain psychiatric disorders—particularly schizophrenia, bipolar disorder, social phobia, panic disorder, personality disorders, and posttraumatic stress disorder—are highly likely to misuse alcohol.[19] It has been proposed that alcohol is utilized as self-medication to relieve psychological distress, psychiatric symptoms, or side effects of medications that are used to treat psychiatric disorders.[20] However, the comorbidity may have a biological basis since psychiatric disorders and AUD share a common neurocircuitry with involvement of the mesolimbic dopamine system and prefrontal cortex.

Chronic heavy alcohol use may result in long-term neuroadaptations that alter motivational and cognitive-control systems and can lead to addiction.[10] Repeated alcohol-induced activation of the motivation-reward system sensitizes it, leading to craving and increased preoccupation with alcohol.[16,17] Over time, the dopaminergic response to natural reinforcers becomes less effective, such that only high doses of alcohol produce reward.[21,22] Chronic alcohol use can result in tolerance to both the unpleasant sedation and the motor impairments that deter alcohol use. This tolerance is created via neuroadaptations that alter

the sensitivity or number of GABA and glutamate neurotransmitter receptors. Tolerance to the unpleasant effects of alcohol may lead to elevated alcohol consumption.

With chronic heavy use of alcohol, the adaptations in glutamate, GABA, and other neurotransmitter systems may become enhanced and produce a hyperexcitable state that balances the sedation produced by alcohol.[23] If alcohol consumption stops during such a state, the neural hyperexcitability is unopposed and leads to signs and symptoms of alcohol withdrawal, including tremors, anxiety, insomnia, and, in severe cases, seizures and delirium. Consuming alcohol again relieves the withdrawal and thus becomes an important factor in maintaining alcohol use.[24]

Recently abstinent chronic alcohol users may experience a protracted, distressing state characterized by anxiety, dysphoria, insomnia, and difficulty coping with stress. This commonly experienced state—known as allostasis—can last for months after cessation of chronic alcohol use. Allostasis is due to a reduction in dopamine response to rewarding stimuli[25] and to hyperresponsiveness in the brain's stress response system, with alterations in central corticotrophin-releasing factor, neuropeptide Y, norepinephrine, dynorphin, and other stress response neurotransmitters.[26] Neurocircuits in the habenula begin to generate negative valance anti-reward signals. Consuming alcohol results in relief of the anti-reward signals, dysphoria, and stress, perpetuating the dysfunction. The enhanced stress response can make stressful situations a powerful precipitant of relapse.[27]

Neuroadaptations due to the chronic use of alcohol enhance craving, defined as a strong and conscious urge or desire to use alcohol. Strong craving for alcohol is difficult to resist. External cues (e.g., sights, sounds, or smells) and internal cues (e.g., anger or sadness) associated with alcohol use can elicit craving for alcohol after prolonged periods of abstinence and can trigger relapse—in particular, early in the posttreatment period.[28]

Alcohol consumption is influenced by cognitive processes, mediated in part by the orbital frontal cortex, cingulate cortex, and insula. The decisional balance to consume or not consume alcohol is a result of the interaction between the brain's motivational and cognitive-control systems. In this regard, awareness of potential adverse consequences of drinking (e.g., potential negative consequences of drinking prior to driving) can inhibit drinking. However, persons with impaired frontal cortical functions—such as those with high trait impulsivity or adolescents with undeveloped frontal cortices—are more likely to drink in spite of potential consequences. Chronic alcohol use results in a loss of metabotropic glutamate receptor 2 (mGluR2) function in the frontal cortex, leading to loss of mGluR2 frontal cortical accumbal inhibition and loss of the ability to inhibit cravings.[29] Chronic alcohol use also enhances brain dynorphin systems that contribute to hippocampal dysfunction, memory problems, and mood dysregulation. These long-term neuroadaptations in cortico-basal ganglia circuits may result in an inability to control alcohol use.[30]

The complexity of the neurotransmitters and circuits that are involved in the development of AUD is reflected in the complex genetics of AUD. Although the heritability of AUD is approximately .4–.6,[31] whether or not an individual develops AUD depends on interactions between multiple risk and protective-risk genes, and with the environment.[32,33] The best-

studied gene that affects the risk of developing substance dependence is the gene that codes for the alcohol-metabolizing enzyme aldehyde dehydrogenase (ALDH). Approximately 40% of individuals in certain Asian populations carry a single nucleotide polymorphism (SNP) variant of the *ALDH* gene (ALDH2*2), which results in altered alcohol metabolism. When persons carrying ALDH2*2 drink alcohol, acetaldehyde—a toxic intermediate of alcohol metabolism—accumulates and produces flushing and nausea. Thus, having this gene variant may be protective against developing AUD.[34] That said, AUD is still present, although at a reduced prevalence, in populations with high frequencies of ALDH2*2.[34] By contrast, a SNP variant of the *GABRA2* gene that codes for the alpha-2 subunit of the GABA-A receptor may increase the risk of developing AUD via reduction of the sedative effects of alcohol. Possession of such a gene may permit carriers to drink larger quantities of alcohol.[35] The heterogeneity in the etiology of AUD suggests that the ideal treatment for AUD may ultimately require personalized pharmacological approaches that target the specific neurobehavioral systems leading to alcohol addiction.

PHARMACOTHERAPIES APPROVED FOR TREATING AUD IN THE UNITED STATES

The following sections discuss the use of pharmacotherapies to treat AUD, focusing on mechanisms of action and evidence for efficacy. The discussion includes FDA-approved medications but also discusses other pharmacotherapies with evidence for efficacy in treating alcoholism that are approved for use outside the United States or are used off-label (see Text Box 1).

Text Box 1

Pharmacotherapies for Alcohol Use Disorder

Pharmacotherapies Approved for Treatment of AUD in the United States
Acamprosate
Disulfiram
Naltrexone (oral)
Naltrexone (extended-release injectable)
Other Pharmacotherapies Approved for Treatment of AUD in the European Union
Gamma-hydroxybutyrate (GHB)
Nalmefene
Medications Under Investigation for Treatment of Alcohol Dependence
Aripiprazole
Baclofen
Buproprion
Gabapentin
Kudzu (isoflavone)
Memantine
Metadoxine
Olanzapine

Ondansetron
Prazosin (alpha-1 antagonist)
Quetiapine
Rimonabant (CB1 receptor antagonist)
SSRIs
Topiramate
Varenicline
Zonisamide

CB1, cannabinoid 1; SSRI, selective serotonin reuptake inhibitor.

Disulfiram

The prototype medication that is used to treat AUD by altering the effects of alcohol intoxication is disulfiram, approved by the FDA in the 1950s. Disulfiram enhances the negative and punishing effects of alcohol by inhibiting acetaldehyde dehydrogenase (the same enzyme affected by the natural ALDH2*2 polymorphism described above) and reduces the risk of developing AUD.[36,37] Inhibiting aldehyde dehydrogenase with disulfiram causes acetaldehyde to accumulate in the blood whenever alcohol is consumed and causes aversive symptoms such as skin flushing, tachycardia, hypotension, sweating, shortness of breath, nausea, and vomiting. The disulfiram-alcohol reaction provides a strong deterrent to alcohol consumption.[38]

Although disulfiram has been used to treat AUD for more than 60 years, few well-controlled studies of its effectiveness as a treatment exist. Studies that have been conducted exhibit mixed results. The largest disulfiram study was a multicenter trial conducted in 605 male veterans with AUD who received either a therapeutic dose of disulfiram, a placebo dose of disulfiram, or a vitamin over the course of a year. The results showed no significant differences in abstinence between groups.[39]

The results of recent studies suggest that improving adherence to disulfiram treatment is necessary for disulfiram to be effective. A six-month randomized, controlled trial (RCT) on disulfiram's effectiveness in improving drinking outcomes was conducted with 126 patients.[40] Patients took either 200 mg disulfiram or 100 mg vitamin C. Subsequently, patients in the disulfiram group reported reductions in drinking alcohol, more abstinent days, and lower gamma-glutamyl transpeptidase levels. In a separate disulfiram study with couples receiving behavioral marital therapy, couples who were asked to enter into a contract for spousal supervision of medication compliance ultimately displayed reductions in alcohol intake as compared to couples in the non-spousal-supervision group.[41] In a 12-week clinical trial of 122 patients with concurrent cocaine use disorder and AUD receiving either disulfiram or no medication (both of which were combined with manualized psychotherapy to improve medication adherence), those receiving disulfiram had better treatment retention and longer abstinence duration for both cocaine and alcohol.[42] Because disulfiram inhibits dopamine-beta-hydroxylase, thereby increasing dopamine levels, disulfiram may reduce craving for both cocaine and alcohol through this mechanism.

Disulfiram can also produce hepatotoxicity and psychosis. Despite its adverse effects and questions regarding its effectiveness, disulfiram can be a useful treatment for some patients, particularly those who are medication compliant.

Naltrexone

Animal research has indicated that opioid antagonists are linked with reductions in alcohol consumption,[43] and related clinical research has reported similar findings. Two 12-week RCTs in patients diagnosed with AUD also showed that patients treated with naltrexone displayed both reductions in heavy drinking and sustained abstinence.[44] In 1994, these findings led the FDA to approve the mu-opioid antagonist naltrexone as an adjunct to psychosocial therapies in treating alcoholism.

Opioid antagonists reduce drinking via several mechanisms. First, they reduce the stimulating and positively reinforcing effects of alcohol by blocking the dopaminergic effects of brain endorphins that are released following alcohol consumption.[45] Endorphins act at mu- and delta-opioid receptors on GABAergic interneurons in the ventral tegmental area to disinhibit these neurons and thereby produce an increased release of dopamine into the nucleus accumbens, amygdala, and forebrain. This effect is blocked by naltrexone and other opioid antagonists. Second, naltrexone appears to enhance the sedative effects of alcohol. Third, opioid antagonists reduce craving for alcohol, both when alcohol is consumed and in response to alcohol cues when alcohol is not consumed.

Several meta-analyses of naltrexone clinical trials for AUD demonstrate consistent effectiveness with modest effect sizes for efficacy (0.15–0.2) in reducing heavy drinking.[46,47] Naltrexone appears less effective in promoting complete abstinence.[48] Evidence for a pharmacogenomic influence in naltrexone's effect on drinking is variable; some studies have observed greater effectiveness in reducing drinking in individuals who carry the Asp40 (118G) allele of the *OPRM1* gene that encodes the mu-opioid receptor.[49,50]

At the usual daily dosage of naltrexone (i.e., 50 mg), approximately 10% of patients experience anxiety, sedation, or nausea. Although hepatotoxicity has been reported at higher (i.e., 300 mg) daily doses,[51] it is rare at the typical 50 mg daily dose, and naltrexone has been used with close monitoring in individuals with liver disease.[52] Patients taking naltrexone are insensitive to opioid analgesia, though the effect wears off within 72 hours following discontinuation of the drug. When opioid analgesics are required immediately, the blockade can be reversed by administering high-dose opioids, followed by careful monitoring and observation. A Treatment Improvement Protocol regarding the use of naltrexone published by the Substance Abuse and Mental Health Services Administration details complete information and treatment guidelines.[52]

To address poor medication adherence with oral naltrexone, a sustained-release, intramuscular naltrexone preparation was developed. It has been shown to reduce heavy drinking and to enhance abstinence, and is FDA approved for treating AUD.[53] A six-month multisite study in 627 non-abstinent adults with AUD found significant dose-related reductions in heavy-drinking rates after administering two doses of sustained-release naltrexone, as compared to placebo (26% at the highest dose).[54] The most frequently

reported adverse events connected with sustained-release naltrexone included headache, injection-site tenderness, fatigue, and nausea (which affected 33%). Occasionally, abscesses occur at the injection site, and their occurrence has given rise to an FDA warning letter. Sustained-release naltrexone may produce less hepatotoxicity than oral naltrexone since the injected sustained-release drug does not undergo first-pass metabolism in the liver.

Acamprosate

Chronic alcohol use alters the activity of neurotransmitters and ion channels in the brain and may result in a compensatory state of excitation. Notably, excitatory glutamate systems are upregulated, and inhibitory GABA systems are downregulated. Acamprosate (calcium N-acetylhomotaurinate), a structural analog of the sulfated amino acid taurine, reduces alcohol consumption in animal models and has also been shown to decrease withdrawal distress and craving in human studies.[55] Its mechanism of action is not completely understood, but acamprosate has inhibitory effects at the metabotropic glutamate receptor 5 (mGluR5)[56] and can reduce the elevated glutamate levels that are observed in individuals with severe AUD. Acamprosate binds to polyamine regulatory sites on NMDA receptors[57] and has both excitatory and inhibitory effects, depending upon experimental conditions.[58,59] In addition, Spanagel and colleagues[60] recently proposed that N-acetylhomotaurinate alone is not an active psychotropic molecule; rather, calcium is the active component, demonstrating anti-relapse effects.

Multiple clinical trials conducted in Europe showed that acamprosate added to psychosocial interventions improved the duration and rate of abstinence. Three European multi-center trials supported the FDA approval of acamprosate to maintain abstinence from alcohol.[61–63] However, two US trials—a 6-month multisite study[64] and the COMBINE Study[65]—and a recent multisite German trial[66] failed to find efficacy for acamprosate. The reasons for the differences in effectiveness are unclear, but it has been suggested that differences in the severity of AUD and in patient characteristics, along with the use of inpatient detoxification in early studies, may explain the divergent results. Despite the variability in study outcomes, two recent meta-analyses showed a small overall positive treatment efficacy, particularly for abstinence as a treatment goal.[48,67]

OTHER PHARMACOTHERAPIES APPROVED FOR TREATING AUD IN THE EUROPEAN UNION

Disulfiram, naltrexone, and acamprosate are approved for treatment in Europe by the European Medications Agency, the counterpart of the United States' FDA. In addition, two other medications—nalmefene and gamma-hydroxybutyrate—are approved and used for AUD treatment in some European countries. These two pharmacotherapies are discussed below.

Nalmefene

Nalmefene is an opioid antagonist initially approved for the reversal of opioid intoxication. It differs from naltrexone due to its partial agonist activity at the kappa-opioid receptor and its reduced hepatotoxicity. Mason and colleagues conducted a clinical trial in 21 participants

with AUD[68] and a follow-up trial in 105 participants with AUD.[69] In both studies nalmefene combined with psychosocial treatment was superior to placebo and psychosocial treatment in decreasing rates of heavy alcohol consumption. Another study, however, reported contrary findings. In a 12-week RCT, 270 abstinent patients diagnosed with AUD were administered either placebo or nalmefene, both in conjunction with motivational enhancement therapy.[70] Nalmefene displayed no significant efficacy. In two additional European studies, 718 and 598 current drinkers with AUD were administered either nalmefene or placebo in a directed or "as needed fashion" (i.e., on specific days when patients perceived they were at elevated risk for alcohol consumption).[13,71] Nalmefene was found effective in decreasing the amount of alcohol consumption and the number of drinking days. Nalmefene is approved for treating AUD in the European Union but not in the United States.

Gamma-Hydroxybutyrate

The sedative medication gamma-hydroxybutyrate (GHB) enhances inhibition at both GABA-A and GABA-B receptors, and is used clinically for treating narcolepsy. GHB was found to be effective for treating AUD in a placebo-controlled clinical trial conducted in Europe.[72] A form of GHB, marketed as sodium oxybate, is approved for AUD treatment in several European countries. It is thought that GHB acts as an alcohol substitute, reducing craving for alcohol and preventing alcohol withdrawal and allostasis. However, the abuse potential of GHB has been noted in some European studies, and the medication is frequently abused in the United States. Thus, GHB requires careful selection of patients who are likely to be adherent to dosing recommendations, and also careful monitoring of its use.[73,74]

NON-FDA-APPROVED PHARMACOTHERAPIES FOR TREATING AUD

Topiramate

Very positive results for treating AUD have been obtained with topiramate, a mixed AMPA-glutamate antagonist that also enhances GABA function, inhibits carbonic anhydrase, and inhibits excitatory sodium and calcium channels.[75–77] In a 12-week trial in 150 patients with AUD receiving medication-adherence therapy, topiramate significantly decreased the number of drinks per day, drinks per drinking day, and number of drinking days, and increased the number of days of abstinence compared to placebo.[78] In a subsequent US multisite, placebo-controlled trial involving 371 men and women with AUD who were titrated up to a daily dose of 300 mg, topiramate showed its efficacy in reducing heavy drinking.[79] Moreover, a recent meta-analysis of topiramate supports the efficacy of this medication in reducing heavy drinking.[47]

Topiramate also shows pharmacogenomic variability in response. In a recent study of 138 heavy drinkers with the goal of drinking reduction, topiramate was effective only in individuals of European ancestry who were homozygotes for the rs2832407 C allele of *GRIK1*, which codes the GluK1 subunit of the glutamate kainate receptor.[80] The same rs2832407 allele was found to moderate topiramate side effects in a study of heavy drinkers.[81] Topiramate side effects can be significant and include memory deficits, sedation, and increased risk of suicide and seizures.[82] Side effects can be minimized through a slow

titration over several weeks and the use of a lower daily dose of 200 mg. Topiramate is not FDA approved for AUD treatment; however, its use is endorsed by the National Institute on Alcohol Abuse and Alcoholism, based on the strong evidence for efficacy. In the Veterans Health Administration system, topiramate is prescribed for AUD more often than naltrexone and acamprosate combined.[83] Zonisamide, an antiepileptic closely related to topiramate, was also found to reduce heavy drinking in a small, placebo-controlled clinical trial with 40 individuals with AUD.[83]

Gabapentin

Gabapentin, an antiepileptic agent that inhibits excitatory calcium channels and stimulates inhibitory GABA-B receptors, has been used successfully to treat alcohol withdrawal and AUD.[84] Gabapentin is reported to reduce alcohol consumption, improve sleep, and decrease alcohol craving in subjects with AUD.[85] In a 12-week RCT conducted in 150 recently abstinent outpatients with AUD, gabapentin was found to reduce drinking significantly.[86] High-dose gabapentin (1800 mg) reduced heavy drinking and craving, and improved sleep more than low-dose gabapentin or placebo. Moreover, a study that compared naltrexone, gabapentin plus naltrexone, and placebo found additive effects of the combination and improvements in sleep in the combined medication group.[87]

Benzodiazepines

Benzodiazepines (e.g., diazepam, chlordiazepoxide) have sedative, anxiolytic, and antiepileptic properties. They bind to a modulatory site on the GABA-A receptor chloride channel complex and partially substitute for alcohol by enhancing inhibitory GABA function, which may have been reduced by chronic alcohol use over time. Benzodiazepines inhibit the central nervous system excitation that occurs in alcohol withdrawal and are the most commonly used medications for alcohol detoxification.[88] However, benzodiazepines are rarely used for the post-detoxification treatment of AUD due to the concerns of developing benzodiazepine dependence and the possibility that benzodiazepines may enhance the risk of alcohol relapse.[89]

Baclofen

Baclofen is a GABA-B receptor agonist used to treat spasticity and has been reported to reduce alcohol consumption.[90] Randomized, double-blind, controlled studies conducted in Italy found that baclofen reduced alcohol drinking in individuals with AUD.[91] Subsequently, a larger placebo-controlled trial in patients with AUD and severe liver cirrhosis demonstrated the efficacy and safety of baclofen to reduce drinking.[92] However, a placebo-controlled clinical trial of baclofen conducted in the United States with 80 patients with AUD did not show effectiveness for baclofen in reducing drinking, although it was effective in reducing anxiety.[93] Baclofen study doses typically range from 20 to 80 mg daily; however, the use of even higher baclofen doses is suggested,[94] though sedation is a major limiting side effect.

Memantine

Given the loss of mGluR2 receptors in AUD and the resulting hyperglutamergic state, medications that block glutamate directly and mGluR agonists that negatively modulate glutamate indirectly may hold promise as pharmacotherapies for AUD treatment. However, results from studies with glutamate antagonists in human subjects with AUD have been mixed. Placebo-controlled clinical trials with memantine, a noncompetitive NMDA antagonist used for treating Alzheimer's disease, have not demonstrated differences between memantine and placebo.[95–97]

Serotonergic and Dopaminergic Pharmacotherapies

Given the importance of dopamine and serotonin neurobiology in AUD, using these medications to treat AUD is of interest. In two separate, 12-week trials of dopamine antagonists, olanzapine reduced alcohol craving and consumption,[98] and quetiapine reduced heavy drinking.[99] However, a subsequent multisite, placebo-controlled trial with quetiapine in heavy-drinking patients with AUD did not show efficacy in reducing drinking.[100] Buspirone is an anxiolytic with serotonin partial agonist effects and antagonist effects at the D2 dopamine receptor. A double-blind, placebo-controlled study in nonanxious patients with AUD failed to show efficacy for buspirone in reducing drinking or craving.[101]

Selective Serotonin Reuptake Inhibitors

Selective serotonin reuptake inhibitors, which augment serotonergic function, are commonly used by patients with AUD to treat depressive and anxious symptoms. Although initial studies suggested that SSRIs reduce alcohol consumption in heavy drinkers by 15%–20%,[102] subsequent placebo-controlled trials in subjects with AUD did not find drinking reductions. A double-blind, placebo-controlled study of fluoxetine found no difference in drinking in nondepressed patients.[103] However, two studies suggested that SSRIs may have efficacy in the Babor Type A subtype of alcoholic, characterized by later age of drinking onset and less severe psychopathology.[104,105]

Ondansetron

Ondansetron, a serotonin-3 receptor antagonist used to treat nausea, was efficacious in subjects with early-onset AUD (i.e., prior to age 25).[106] A more recent study demonstrated ondansetron's efficacy in 283 patients with AUD and who had variants in *SLC6A4* (the gene encoding the serotonin transporter promoter [5-HTTLPR])—including the long (L) and short versions of a variable number of tandem repeats—and a separate rs1042173 SNP.[107] Patients with AUD and the long LL genotype of the serotonin transporter promoter significantly reduced their drinking, and those who also carried the TT genotype of the SNP reduced their drinking even more. These findings with ondansetron were partially corroborated in a recent study with 77 non-treatment-seeking subjects with AUD that showed that those with the LL allele significantly reduced their drinking.[106] These studies demonstrate the heterogeneity of AUD and the need for a personalized approach to pharmacological treatment with serotonergic medications.

Varenicline

Varenicline is an FDA approved medication for smoking cessation with potential use as a pharmacotherapy for AUD in individuals who smoke.[108] Varenicline is a partial agonist at α4β2, α3β2, and α6 nicotinic acetylcholine receptors (nAChRs), and an agonist of α3β4 and α7 nAChRs.[109–112] NAChRs have been implicated in nicotine- and alcohol-related reward in animal models.[113,114] During a human laboratory self-administration paradigm with heavy-drinking smokers, varenicline produced a greater decrease than placebo in alcohol craving, consumption, and pleasant subjective effects of alcohol.[115] Recent laboratory investigations of the effectiveness of varenicline in reducing craving and consumption of alcohol have produced similar findings,[116] citing decreased alcohol consumption in smokers following varenicline treatment.[108,117] Litten and colleagues[118] conducted the first double-blind, placebo-controlled, multisite clinical trial to assess the efficacy and safety profile of varenicline in a sample of smokers and nonsmokers with AUD. Compared to a placebo group, the group who received varenicline reported a lower weekly percentage of heavy-drinking days, fewer drinks per drinking day, and reduced craving for alcohol. Importantly, the average effect of treatment on alcohol use was similar for both smokers and non-smokers, indicating that varenicline may be an effective pharmacotherapy for individuals who do and do not smoke.

Rimonabant

Cannabinoids have behavioral effects because they mimic the action of the naturally occurring lipid-signaling molecules anandamide and 2-arachidonylglycerol (2-AG) at brain cannabinoid receptors.[118] Cannabinoid CB1 receptors are expressed in the brain reward circuit and modulate the dopamine-releasing effects of alcohol and nicotine. The C allele of rs2023239 is associated with greater CB1 binding in the pre-frontal cortex, greater alcohol cue-elicited brain activation in the midbrain and prefrontal cortex, and greater subjective reward when consuming alcohol.[119] Administration of the cannabinoid receptor antagonist, SR141716A (rimonabant), can decrease voluntary ethanol intake in mice[120] and in alcohol-preferring rats,[121] suggesting that SR141716A may have clinical utility in treating AUD. However, studies of rimonabant in humans with AUD have been disappointing. A double-blind, placebo-controlled study of rimonabant in non-treatment-seeking drinkers with AUD showed no reduction either in naturalistic drinking or in drinking in a controlled laboratory setting.[122] A double-blind, placebo-controlled clinical trial of rimonabant conducted in 258 European subjects with AUD showed no benefit of rimonabant in rate of relapse or of relapse to heavy drinking compared to placebo.[123]

FUTURE POTENTIAL PHARMACOLOGICAL TREATMENTS FOR AUD

Kudzu

The kudzu plant has been used historically in Chinese herbal medicine to reduce the effects of alcohol consumption and to treat alcohol-related problems. The precise mechanism of action of kudzu extract is unclear. Some research suggests that flavonoids (isoflavones) in the kudzu plant (i.e., puerarin, daidzin, daidzein) may decrease consumption of alcohol by modifying aldehyde dehydrogenase (ALDH2) or monoamine oxidase-acetaldehyde pathways.[124] Following alcohol consumption, kudzu extract appears to contribute to a faster

increase in blood alcohol level, likely resulting in more rapid entry of alcohol to the central nervous system, effectively increasing alcohol-related reward from the first drink during an episode.[125] Consequently, elevated alcohol-related reward following the first drink may increase the time to a subsequent drink. Seven-day treatment with a kudzu extract preparation has been shown to significantly decrease consumption of alcohol in the laboratory among heavy drinkers.[126] A recent double-blind, placebo-controlled study that included four weeks of pretreatment with kudzu extract produced a moderate decrease in alcohol consumption among male non-treatment-seeking heavy drinkers.[127] Furthermore, seven-day pretreatment with only one of the three isoflavones in the kudzu plant (puerarin) produced a reduction in consumed drinks during a laboratory alcohol administration session.[128] Drinking topography was also altered following pretreatment with puerarin, with reductions reported in sip size, and increases in number of sips, time to finish a beverage, and latency to begin drinking a subsequent beverage. At this time, Kudzu isoflavones are not FDA approved.

Metadoxine

Research suggests that evaluation of the role of micro- and macronutrients (e.g., magnesium, folic acid, thiamine) may be of great importance in treating AUD since some compounds have been shown to influence abstinence or reduction in alcohol consumption. One such compound, metadoxine (pyridoxol L-2-pyrrolidone-5-carboxylate), is the ion-pair between pyrrolidone carboxylate and pyridoxine[129] and may produce reductions in blood alcohol level by increasing the rate of urinary elimination of ethanol and acetaldehyde.[130] A problem with several approved pharmacotherapies for AUD is that they are capable of inducing hepatotoxicity[131] and thus cannot be administered to individuals with liver diseases. That is, the metabolism of drugs by the liver is a key limitation to the use of various pharmacotherapies for AUD since chronic alcohol consumption contributes to a plethora of alcoholic liver diseases.[132] In this context, metadoxine is a promising novel pharmacotherapy for AUD—in particular, in patients with alcoholic liver disease since it appears to produce improvement in some biomarkers linked with alcohol-related liver damage.[133] Moreover, several studies indicate that metadoxine increases the rate of elimination of alcohol from the blood, resulting in expedited recovery from intoxication and associated symptoms.[129] Compared to control patients, individuals treated with metadoxine display better treatment outcomes (i.e., abstinence and study completion) at three months posttreatment.[134]

Ghrelin Antagonists

In addition to reducing alcohol use, several AUD pharmacotherapies (e.g., naltrexone, topiramate, varenicline, baclofen, rimonabant) can cause weight loss and decreased food consumption, suggesting that they may all have the capacity to reduce consumption by decreasing appetitive drive.[135] Ghrelin, a 28–amino acid peptide that induces hunger for food when secreted by the stomach, has attracted particular interest. In two different studies on treatment-seeking subjects with AUD, baseline ghrelin blood levels were positively correlated with alcohol craving.[136,137] Non-treatment-seeking persons with AUD who received either placebo or one of two different doses of intravenous ghrelin showed increased alcohol craving in response to alcohol cues when they received ghrelin.[138] These

findings that associate ghrelin with alcohol consumption and craving suggest that blocking ghrelin could reduce alcohol consumption. Indeed, rats receiving a ghrelin receptor antagonist, JMV2959, decreased their alcohol drinking when reexposed to alcohol after a period of deprivation.[139] Studies with ghrelin antagonists are ongoing in humans with AUD.

Pharmacotherapies That Reduce Stress Responses

Because AUD is characterized by an enhancement of brain stress response mechanisms,[26] a number of pharmacotherapies that block physiological stress responses have been studied as potential treatments. Agents that block central corticotrophin-releasing hormone receptors reliably reduce alcohol consumption in several animal models of AUD[140] and are being studied in human subjects with AUD.

Steroid hormones, including cortisol and progesterone, are important mediators of the stress response. Alcohol releases cortisol and increases the synthesis of brain neurosteroids. Agents that block the action of steroids, such as the synthesis inhibitor finasteride and the progesterone receptor antagonist mifepristone, reduce alcohol consumption in animals.[141] Finasteride was recently reported to reduce alcohol consumption in humans taking the drug for hair loss.[142] The testing of mifepristone in human subjects with AUD is in early stages.

Norepinephrine mediates both central and peripheral sympathetic stress responses. The alpha-1 adrenergic antagonist prazosin reduces stress symptoms in posttraumatic stress disorder and also appears to reduce alcohol consumption. A small placebo-controlled trial of prazosin in 24 subjects with AUD found significant reductions in drinking.[143] Prazosin also blocks craving induced by alcohol cues and stress.[144]

SUMMARY AND CONCLUSIONS

This article has summarized the neurobiology of AUD and discussed approved and emerging pharmacotherapies in its treatment. Adding adjunctive pharmacological treatment to traditional psychosocial treatments can significantly improve treatment success, but overall the effects are modest, with numbers needed to treat in the range of 10 and effect sizes in the range of 0.1–0.3. The modest effects of pharmacotherapies may partly contribute to the low rate of adoption of the pharmacotherapies into treatment.[145] Pharmacotherapies are certainly not magic bullets that cure AUD; however, they may provide treatment benefits for some patients over and above the benefits of psychosocial treatment alone. Treatment outcomes for patients treated with naltrexone, topiramate, SSRIs, and ondansetron can be improved by targeting those treatments toward specific alcohol subtypes and genetic markers. Improving the effectiveness of pharmacotherapies will therefore likely require a personalized approach, utilizing medications that are targeted at different patient characteristics and genetics. Moreover, the heterogeneity and complexity of AUD may require that future pharmacotherapy treatments target specific physiological and neurobehavioral systems that initiate and maintain AUD—including alcohol metabolism and brain circuits that mediate reinforcement, stress and distress, attention, and decision making. Improved, optimally targeted pharmacotherapies have the potential to improve treatment outcomes and to reduce the individual and public health consequences of AUD. To achieve this potential, more research is required.

References

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5. Arlington, VA: American Psychiatric Publishing; 2013.
2. Hasin DS, O'Brien CP, Auriacombe M, et al. DSM-5 criteria for substance use disorders: recommendations and rationale. Am J Psychiatry. 2013; 170:834–51. [PubMed: 23903334]
3. National Institute on Alcohol Abuse and Alcoholism. Tenth special report to the US Congress on alcohol and health. Washington, DC: US Department of Health and Human Services; 2000. http://pubs.niaaa.nih.gov/publications/10report/chap01.pdf
4. Bouchery EE, Harwood HJ, Sacks JJ, Simon CJ, Brewer RD. Economic costs of excessive alcohol consumption in the U.S. 2006. Am J Prev Med. 2011; 41:516–24. [PubMed: 22011424]
5. Swift RM. Drug therapy for alcohol dependence. N Engl J Med. 1999; 340:1482–90. [PubMed: 10320388]
6. Miller WR, Walters ST, Bennett ME. How effective is alcoholism treatment in the United States? J Stud Alcohol. 2001; 6:211–20. [PubMed: 11327187]
7. Dawson DA, Grant BF, Stinson FS, Chou PS, Huang B, Ruan WJ. Recovery from DSM-IV alcohol dependence: United States, 2001–2002. Addiction. 2005; 100:281–92. [PubMed: 15733237]
8. Kline-Simon AH, Falk DE, Litten RZ, et al. Posttreatment low-risk drinking as a predictor of future drinking and problem outcomes among individuals with alcohol use disorders. Alcohol Clin Exp Res. 2013; 37(suppl 1):E373–80. [PubMed: 22827502]
9. Miller WR, Wilbourne PL. Mesa Grande: a methodological analysis of clinical trials of treatments for alcohol use disorders. Addiction. 2002; 97:265–77. [PubMed: 11964100]
10. Koob GF, Volkow ND. Neurocircuitry of addiction. Neuropsychopharmacology. 2010; 35:217–38. [PubMed: 19710631]
11. McLellan AT, Lewis DC, O'Brien CP, Kleber HD. Drug dependence, a chronic medical illness: implications for treatment, insurance, and outcomes evaluation. JAMA. 2000; 284:1689–95. [PubMed: 11015800]
12. Litten RZ, Egli M, Heilig M, et al. Medications development to treat alcohol dependence: a vision for the next decade. Addict Biol. 2012; 17:513–27. [PubMed: 22458728]
13. Mann K, Bladström A, Torup L, Gual A, van den Brink W. Extending the treatment options in alcohol dependence: a randomized controlled study of as-needed nalmefene. Biol Psychiatry. 2013; 73:706–13. [PubMed: 23237314]
14. Chick J, Nutt DJ. Substitution therapy for alcoholism: time for a reappraisal? J Psychopharmacol. 2012; 26:205–12. [PubMed: 21742726]
15. Kauer JA. Learning mechanisms in addiction: synaptic plasticity in the ventral tegmental area as a result of exposure to drugs of abuse. Annu Rev Physiol. 2004; 66:447–75. [PubMed: 14977410]
16. Robinson TE, Berridge KC. The neural basis of drug craving: an incentive-sensitization theory of addiction. Brain Res Brain Res Rev. 1993; 18:247–91. [PubMed: 8401595]
17. Ray LA, Hutchison KE, MacKillop J, et al. Effects of naltrexone during the descending limb of the blood alcohol curve. Am J Addict. 2008; 17:257–64. [PubMed: 18612879]
18. Morton GJ, Meek TH, Schwartz MW. Neurobiology of food intake in health and disease. Nat Rev Neurosci. 2014; 15:367–78. [PubMed: 24840801]
19. Regier DA, Farmer ME, Rae DS, et al. Comorbidity of mental disorders with alcohol and other drug abuse. Results from the Epidemiologic Catchment Area (ECA) Study. JAMA. 1990; 264:2511–8. [PubMed: 2232018]
20. Khantzian EJ. The self-medication hypothesis of addictive disorders: focus on heroin and cocaine dependence. Am J Psychiatry. 1985; 142:1259–64. [PubMed: 3904487]
21. Blum K, Sheridan PJ, Wood RC, et al. The D2 dopamine receptor gene as a determinant of reward deficiency syndrome. J R Soc Med. 1996; 89:396–400. [PubMed: 8774539]
22. Volkow ND, Fowler JS, Wang G-J, Swanson JM, Telang F. Dopamine in drug abuse and addiction: results of imaging studies and treatment implications. Arch Neurol. 2007; 64:1575–9. [PubMed: 17998440]

23. Clapp P, Bhave SV, Hoffman PL. How adaptation of the brain to alcohol leads to dependence: a pharmacological perspective. Alcohol Res Health. 2008; 31:310–99. [PubMed: 20729980]
24. Littleton J. Neurochemical mechanisms underlying alcohol withdrawal. Alcohol Health Res World. 1998; 22:13–24. [PubMed: 15706728]
25. Koob GF, Le Moal M. Drug addiction, dysregulation of reward, and allostasis. Neuropsychopharmacology. 2001; 24:97–129. [PubMed: 11120394]
26. Koob GF. A role for brain stress systems in addiction. Neuron. 2008; 59:11–34. [PubMed: 18614026]
27. Heilig M, Egli M, Crabbe JC, Becker HC. Acute withdrawal, protracted abstinence and negative affect in alcoholism: are they linked? Addict Biol. 2010; 15:169–84. [PubMed: 20148778]
28. Rohsenow DJ, Monti PM, Rubonis AV, et al. Cue exposure with coping skills training and communication skills training for alcohol dependence: 6- and 12-month outcomes. Addiction. 2001; 96:1161–74. [PubMed: 11487422]
29. Meinhardt MW, Hansson AC, Perreau-Lenz S, et al. Rescue of infralimbic mGluR2 deficit restores control over drug-seeking behavior in alcohol dependence. J Neurosci. 2013; 33:2794–806. [PubMed: 23407939]
30. Probst CC, van Eimeren T. The functional anatomy of impulse control disorders. Curr Neurol Neurosci Rep. 2013; 13:386. [PubMed: 23963609]
31. Heath AC. Genetic influences on alcoholism risk. A review on adoption and twin studies. Alcohol Health Res World. 1995; 19:166–71.
32. Strat YL, Ramoz N, Schumann G, Gorwood P. Molecular genetics of alcohol dependence and related endophenotypes. Curr Genomics. 2008; 9:444–51. [PubMed: 19506733]
33. Foroud T, Edenberg HJ, Crabbe JC. Genetic research: who is at risk for alcoholism. Alcohol Res Health. 2010; 33:64–75. [PubMed: 23579937]
34. Higuchi S, Matsushita S, Murayama M, Takagi S, Hayashida M. Alcohol and aldehyde dehydrogenase polymorphisms and the risk for alcoholism. Am J Psychiatry. 1995; 152:1219–21. [PubMed: 7625477]
35. Das S, Harel O, Dey DK, Covault J, Kranzler HR. Analysis of extreme drinking in patients with alcohol dependence using Pareto regression. Stat Med. 2010; 29:1250–8. [PubMed: 20225194]
36. Wall TL. Genetic associations of alcohol and aldehyde dehydrogenase with alcohol dependence and their mechanisms of action. Ther Drug Monit. 2005; 27:700–3. [PubMed: 16404797]
37. Thomasson HR, Edenberg HJ, Crabb DW, et al. Alcohol and aldehyde dehydrogenase genotypes and alcoholism in Chinese men. Am J Hum Genet. 1991; 48:677–81. [PubMed: 2014795]
38. Suh JJ, Pettinati HM, Kampman KM, O'Brien CP. The status of disulfiram: a half of a century later. J Clin Psychopharmacol. 2006; 26:290–302. [PubMed: 16702894]
39. Fuller RK, Branchey L, Brightwell DR, et al. Disulfiram treatment of alcoholism. A Veterans Administration cooperative study. JAMA. 1986; 256:1449–55. [PubMed: 3528541]
40. Chick J, Gough K, Falkowski W, et al. Disulfiram treatment of alcoholism. Br J Psychiatry. 1992; 161:84–9. [PubMed: 1638335]
41. O'Farrell TJ, Allen JP, Litten RZ. Disulfiram (antabuse) contracts in treatment of alcoholism. NIDA Res Monogr. 1995; 150:65–91. [PubMed: 8742773]
42. Carroll KM, Nich C, Ball SA, McCance E, Rounsavile BJ. Treatment of cocaine and alcohol dependence with psychotherapy and disulfiram. Addiction. 1998; 93:713–27. [PubMed: 9692270]
43. Volpicelli JR, Alterman AI, Hayashida M, O'Brien CP. Naltrexone in the treatment of alcohol dependence. Arch Gen Psychiatry. 1992; 49:876–80. [PubMed: 1345133]
44. O'Malley SS, Jaffe AJ, Chang G, Schottenfeld RS, Meyer RE, Rounsaville B. Naltrexone and coping skills therapy for alcohol dependence. A controlled study. Arch Gen Psychiatry. 1992; 49:881–7. [PubMed: 1444726]
45. Swift RM, Whelihan W, Kuznetsov O, Buongiorno G, Hsuing H. Naltrexone-induced alterations in human ethanol intoxication. Am J Psychiatry. 1994; 151:1463–7. [PubMed: 8092339]
46. Rösner S, Hackl-Herrwerth A, Leucht S, Vecchi S, Srisurapanont M, Soyka M. Opioid antagonists for alcohol dependence. Cochrane Database Syst Rev. 2010; (12):CD001867. [PubMed: 21154349]

47. Jonas DE, Amick HR, Feltner C, et al. Pharmacotherapy for adults with alcohol use disorders in outpatient settings: a systematic review and meta-analysis. JAMA. 2014; 311:1889–900. [PubMed: 24825644]

48. Rösner S, Leucht S, Lehert P, Soyka M. Acamprosate supports abstinence, naltrexone prevents excessive drinking: evidence from a meta-analysis with unreported outcomes. J Psychopharmacol. 2008; 22:11–23. [PubMed: 18187529]

49. Oslin DW, Berrettini W, Kranzler HR, et al. A functional polymorphism of the muopioid receptor gene is associated with naltrexone response in alcohol-dependent patients. Neuropsychopharmacology. 2003; 28:1546–52. [PubMed: 12813472]

50. Anton RF, Oroszi G, O'Malley S, et al. An evaluation of mu-opioid receptor (OPRM1) as a predictor of naltrexone response in the treatment of alcohol dependence: results from the Combined Pharmacotherapies and Behavioral Interventions for Alcohol Dependence (COMBINE) study. Arch Gen Psychiatry. 2008; 65:135–44. [PubMed: 18250251]

51. Pfohl DN, Allen JI, Atkinson RL, et al. Naltrexone hydrochloride (Trexan): a review of serum transaminase elevations at high dosage. NIDA Res Monogr. 1986; 67:66–72. [PubMed: 3092099]

52. Center for Substance Abuse Treatment. Treatment Improvement Protocol (TIP) series. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2009. Incorporating alcohol pharmacotherapies into medical practice.

53. U.S. Food and Drug Administration. News & events: FDA approves injectable drug to treat opioid-dependent patients. Oct 12. 2010 http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm229109.htm

54. Garbutt JC, Kranzler HR, O'Malley SS, et al. Efficacy and tolerability of long-acting injectable naltrexone for alcohol dependence: a randomized controlled trial. JAMA. 2005; 293:1617–25. [PubMed: 15811981]

55. Littleton J. Acamprosate in alcohol dependence: how does it work? Addiction. 1995; 90:1179–88. [PubMed: 7580816]

56. Harris BR, Prendergast MA, Gibson DA, et al. Acamprosate inhibits the binding and neurotoxic effects of trans-ACPD, suggesting a novel site of action at metabotropic glutamate receptors. Alcohol Clin Exp Res. 2002; 26:1779–93. [PubMed: 12500101]

57. Naassila M, Hammoumi S, Legrand E, Durbin P, Daoust M. Mechanism of action of acamprosate. Part I. Characterization of spermidine-sensitive acamprosate binding site in rat brain. Alcohol Clin Exp Res. 1998; 22:802–9. [PubMed: 9660304]

58. Berton F, Francesconi WG, Madamba SG, Zieglgänsberger W, Siggins GR. Acamprosate enhances N-methyl-D-apartate receptor-mediated neurotransmission but inhibits presynaptic GABA(B) receptors in nucleus accumbens neurons. Alcohol Clin Exp Res. 1998; 22:183–91. [PubMed: 9514305]

59. Madamba SG, Schweitzer P, Zieglgänsberger W, Siggins GR. Acamprosate (calcium acetylhomotaurinate) enhances the N-methyl-D-aspartate component of excitatory neurotransmission in rat hippocampal CA1 neurons in vitro. Alcohol Clin Exp Res. 1996; 20:651–8. [PubMed: 8800380]

60. Spanagel R, Vengeliene V, Jandeleit B, et al. Acamprosate produces its anti-relapse effects via calcium. Neuropsychopharmacology. 2014; 39:783–91. [PubMed: 24081303]

61. Paille FM, Guelfi JD, Perkins AC, Royer RJ, Steru L, Parot P. Double-blind randomized multicentre trial of acamprosate in maintaining abstinence from alcohol. Alcohol Alcohol. 1995; 30:239–47. [PubMed: 7662044]

62. Pelc I, Verbanck P, Le Bon O, Gavrilovic M, Lion K, Lehert P. Efficacy and safety of acamprosate in the treatment of detoxified alcohol-dependent patients. A 90-day placebo-controlled dose-finding study. Br J Psychiatry. 1997; 171:73–7. [PubMed: 9328500]

63. Sass H, Soyka M, Mann K, Zieglgänsberger W. Relapse prevention by acamprosate. Results from a placebo-controlled study on alcohol dependence. Arch Gen Psychiatry. 1996; 53:673–80. [PubMed: 8694680]

64. Mason BJ, Goodman AM, Chabac S, Lehert P. Effect of oral acamprosate on abstinence in patients with alcohol dependence in a double-blind, placebo-controlled trial: the role of patient motivation. J Psychiatr Res. 2006; 40:383–93. [PubMed: 16546214]

65. Anton RF, O'Malley SS, Ciraulo DA, et al. Combined pharmacotherapies and behavioral interventions for alcohol dependence: the COMBINE study: a randomized controlled trial. JAMA. 2006; 295:2003–17. [PubMed: 16670409]

66. Mann K, Lemenager T, Hoffmann S, et al. Results of a double-blind, placebo-controlled pharmacotherapy trial in alcoholism conducted in Germany and comparison with the US COMBINE study. Addict Biol. 2013; 18:937–46. [PubMed: 23231446]

67. Maisel NC, Blodgett JC, Wilbourne PL, Humphreys K, Finney JW. Meta-analysis of naltrexone and acamprosate for treating alcohol use disorders: when are these medications most helpful? Addiction. 2013; 108:275–93. [PubMed: 23075288]

68. Mason BJ, Ritvo EC, Morgan RO, et al. A double-blind, placebo-controlled pilot study to evaluate the efficacy and safety of oral nalmefene HCl for alcohol dependence. Alcohol Clin Exp Res. 1994; 18:1162–7. [PubMed: 7847600]

69. Mason BJ, Salvato FR, Williams LD, Ritvo EC, Cutler RB. A double-blind, placebo-controlled study of oral nalmefene for alcohol dependence. Arch Gen Psychiatry. 1999; 56:719–24. [PubMed: 10435606]

70. Anton RF, Pettinati H, Zweben A, et al. A multi-site dose ranging study of nalmefene in the treatment of alcohol dependence. J Clin Psychopharmacol. 2004; 24:421–8. [PubMed: 15232334]

71. Gual A, He Y, Torup L, van den Brink W, Mann K. ESENSE 2 Study Group. A randomised, double-blind, placebo-controlled, efficacy study of nalmefene, as-needed use, in patients with alcohol dependence. Eur Neuropsychopharmacol. 2013; 23:1432–42. [PubMed: 23562264]

72. Addolorato G, Castelli E, Stefanini GF, et al. An open multicentric study evaluating 4-hydroxybutyric acid sodium salt in the medium-term treatment of 179 alcohol dependent subjects. Alcohol Alcohol. 1996; 31:341–5. [PubMed: 8879280]

73. Caputo F. Gamma-hydroxybutyrate (GHB) for the treatment of alcohol dependence: a call for further understanding. Alcohol Alcohol. 2011; 46:3. [PubMed: 21109543]

74. Addolorato G, Caputo F, Capristo E, Stefanini GF, Gasbarrini G. Gamma-hydroxybutyric acid efficacy, potential abuse, and dependence in the treatment of alcohol addiction. Alcohol. 2000; 20:217–22. [PubMed: 10869862]

75. Zhang X, Velumian AA, Jones OT, Carlen PL. Modulation of high-voltage-activated calcium channels in dentate granule cells by topiramate. Epilepsia. 2000; 41(suppl 1):S52–60. [PubMed: 10768302]

76. White HS, Brown SD, Woodhead JH, Skeen GA, Wolf HH. Topiramate modulates GABA-evoked currents in murine cortical neurons by a nonbenzodiazepine mechanism. Epilepsia. 2000; 41(suppl 1):S17–20. [PubMed: 10768294]

77. Dodgson SJ, Shank RP, Maryanoff BE. Topiramate as an inhibitor of carbonic anhydrase isoenzymes. Epilepsia. 2000; 41(suppl 1):S35–9. [PubMed: 10768298]

78. Johnson BA, Ait-Daoud N, Bowden CL, et al. Oral topiramate for treatment of alcohol dependence: a randomised controlled trial. Lancet. 2003; 361:1677–85. [PubMed: 12767733]

79. Johnson BA, Rosenthal N, Capece JA, et al. Topiramate for treating alcohol dependence: a randomized controlled trial. JAMA. 2007; 298:1641–51. [PubMed: 17925516]

80. Kranzler HR, Covault J, Feinn R, et al. Topiramate treatment for heavy drinkers: moderation by a GRIK1 polymorphism. Am J Psychiatry. 2014; 171:445–52. [PubMed: 24525690]

81. Ray LA, Miranda R Jr, MacKillop J, et al. A preliminary pharmacogenetic investigation of adverse events from topiramate in heavy drinkers. Exp Clin Psychopharmacol. 2009; 17:122–9. [PubMed: 19331489]

82. Ortinski P, Meador KJ. Cognitive side effects of antiepileptic drugs. Epilepsy Behav. 2004; 5(suppl 1):S60–5. [PubMed: 14725848]

83. Del Re AC, Gordon AJ, Lembke A, Harris AH. Prescription of topiramate to treat alcohol use disorders in the Veterans Health Administration. Addict Sci Clin Pract. 2013; 8:12. [PubMed: 23835352]

84. Myrick H, Malcolm R, Randall PK, et al. A double-blind trial of gabapentin versus lorazepam in the treatment of alcohol withdrawal. Alcohol Clin Exp Res. 2009; 33:1582–8. [PubMed: 19485969]

85. Mason BJ, Light JM, Williams LD, Drobes DJ. Proof-of-concept human laboratory study for protracted abstinence in alcohol dependence: effects of gabapentin. Addict Biol. 2009; 14:73–83. [PubMed: 18855801]

86. Mason BJ, Quello S, Goodell V, Shadan F, Kyle M, Begovic A. Gabapentin treatment for alcohol dependence: a randomized clinical trial. JAMA. 2014; 174:70–7.

87. Anton RF, Myrick H, Wright TM, et al. Gabapentin combined with naltrexone for the treatment of alcohol dependence. Am J Psychiatry. 2011; 168:709–17. [PubMed: 21454917]

88. Mayo-Smith MF. Pharmacological management of alcohol withdrawal. A meta-analysis and evidence-based practice guideline. American Society of Addiction Medicine Working Group on Pharmacological Management of Alcohol Withdrawal. JAMA. 1997; 278:144–51. [PubMed: 9214531]

89. Zack M, Poulos CX, Woodford TM. Diazepam dose-dependently increases or decreases implicit priming of alcohol associations in problem drinkers. Alcohol Alcohol. 2006; 41:604–10. [PubMed: 17020910]

90. Brennan JL, Leung JG, Gagliardi JP, Rivelli SK, Muzyk AJ. Clinical effectiveness of baclofen for the treatment of alcohol dependence: a review. Clin Pharmacol. 2013; 5:99–107. [PubMed: 23869179]

91. Addolorato G, Caputo F, Capristo E, et al. Baclofen efficacy in reducing alcohol craving and intake: a preliminary double-blind randomized controlled study. Alcohol Alcohol. 2002; 37:504–8. [PubMed: 12217947]

92. Addolorato G, Leggio L, Ferrulli A, et al. Effectiveness and safety of baclofen for maintenance of alcohol abstinence in alcohol-dependent patients with liver cirrhosis: randomised, double-blind controlled study. Lancet. 2007; 370:1915–22. [PubMed: 18068515]

93. Garbutt JC, Kampov-Polevoy AB, Gallop R, Kalka-Juhl L, Flannery BA. Efficacy and safety of baclofen for alcohol dependence: a randomized, double-blind, placebo-controlled trial. Alcohol Clin Exp Res. 2010; 34:1849–57. [PubMed: 20662805]

94. Ameisen O. High-dose baclofen for suppression of alcohol dependence. Alcohol Clin Exp Res. 2011; 35:845–6. author reply 847. [PubMed: 21303382]

95. Evans SM, Levin FR, Brooks DJ, Garawi F. A pilot double-blind treatment trial of memantine for alcohol dependence. Alcohol Clin Exp Res. 2007; 31:775–82. [PubMed: 17378918]

96. Muhonen LH, Lönnqvist J, Juva K, Alho H. Double-blind, randomized comparison of memantine and escitalopram for the treatment of major depressive disorder comorbid with alcohol dependence. J Clin Psychiatry. 2008; 69:392–9. [PubMed: 18348597]

97. Sani G, Serra G, Kotzalidis GD, et al. The role of memantine in the treatment of psychiatric disorders other than the dementias: a review of current preclinical and clinical evidence. CNS Drugs. 2012; 26:663–90. [PubMed: 22784018]

98. Hutchison KE, Ray L, Sandman E, et al. The effect of olanzapine on craving and alcohol consumption. Neuropsychopharmacology. 2006; 31:1310–7. [PubMed: 16237394]

99. Kampman KM, Pettinati HM, Lynch KG, et al. A double-blind, placebo-controlled pilot trial of quetiapine for the treatment of Type A and Type B alcoholism. J Clin Psychopharmacol. 2007; 27:344–51. [PubMed: 17632217]

100. Litten RZ, Fertig JB, Falk DE, et al. A double-blind, placebo-controlled trial to assess the efficacy of quetiapine fumarate XR in very heavy-drinking alcohol-dependent patients. Alcohol Clin Exp Res. 2012; 36:406–16. [PubMed: 21950727]

101. Malec E, Malec T, Gagné MA, Dongier M. Buspirone in the treatment of alcohol dependence: a placebo-controlled trial. Alcohol Clin Exp Res. 1996; 20:307–12. [PubMed: 8730222]

102. Naranjo CA, Bremner KE. Clinical pharmacology of serotonin-altering medications for decreasing alcohol consumption. Alcohol Alcohol. 1993; 2:221–9.

103. Kranzler HR, et al. Placebo-controlled trial of fluoxetine as an adjunct to relapse prevention in alcoholics. Am J Psychiatry. 1995; 152:391–7. [PubMed: 7864265]

104. Kranzler HR, Feinn R, Armeli S, Tennen H. Comparison of alcoholism subtypes as moderators of the response to sertraline treatment. Alcohol Clin Exp Res. 2012; 36:509–16. [PubMed: 21895712]

105. Pettinati HM, Volpicelli JR, Kranzler HR, Luck G, Rukstalis MR, Cnaan A. Sertraline treatment for alcohol dependence: interactive effects of medication and alcoholic subtype. Alcohol Clin Exp Res. 2000; 24:1041–9. [PubMed: 10924008]

106. Johnson BA, Roache JD, Javors MA, et al. Ondansetron for reduction of drinking among biologically predisposed alcoholic patients: a randomized controlled trial. JAMA. 2000; 284:963–71. [PubMed: 10944641]

107. Johnson BA, Seneviratne C, Wang X-Q, Ait-Daoud N, Li MD. Determination of genotype combinations that can predict the outcome of the treatment of alcohol dependence using the 5-HT(3) antagonist ondansetron. Am J Psychiatry. 2013; 170:1020–31. [PubMed: 23897038]

108. Fucito LM, Toll BA, Wu R, Romano DM, Tek E, O'Malley SS. A preliminary investigation of varenicline for heavy drinking smokers. Psychopharmacology (Berl). 2011; 215:655–63. [PubMed: 21221531]

109. Coe JW, Brooks PR, Vetelino MG, et al. Varenicline: an alpha4beta2 nicotinic receptor partial agonist for smoking cessation. J Med Chem. 2005; 48:3474–7. [PubMed: 15887955]

110. Davis TJ, de Fiebre CM. Alcohol's actions on neuronal nicotinic acetylcholine receptors. Alcohol Res Health. 2006; 29:179–85. [PubMed: 17373406]

111. Obach RS, Reed-Hagen AE, Krueger SS, et al. Metabolism and disposition of varenicline, a selective alpha4beta2 acetylcholine receptor partial agonist, in vivo and in vitro. Drug Metab Dispos. 2006; 34:121–30. [PubMed: 16221753]

112. Rollema H, Coe JW, Chambers LK, Hurst RS, Stahl SM, Williams KE. Rationale, pharmacology and clinical efficacy of partial agonists of alpha4beta2 nACh receptors for smoking cessation. Trends Pharmacol Sci. 2007; 28:316–25. [PubMed: 17573127]

113. Ericson M, Löf E, Stomberg R, Söderpalm B. The smoking cessation medication varenicline attenuates alcohol and nicotine interactions in the rat mesolimbic dopamine system. J Pharmacol Exp Ther. 2009; 329:225–30. [PubMed: 19126781]

114. Lê AD, Corrigall WA, Harding JW, Juzytsch W, Li TK. Involvement of nicotinic receptors in alcohol self-administration. Alcohol Clin Exp Res. 2000; 24:155–63. [PubMed: 10698366]

115. McKee SA, Harrison EL, O'Malley SS, et al. Varenicline reduces alcohol self-administration in heavy-drinking smokers. Biol Psychiatry. 2009; 66:185–90. [PubMed: 19249750]

116. Nocente R, Vitali M, Balducci G, Enea D, Kranzler HR, Ceccanti M. Varenicline and neuronal nicotinic acetylcholine receptors: a new approach to the treatment of co-occurring alcohol and nicotine addiction? Am J Addict. 2013; 22:453–9. [PubMed: 23952890]

117. Mitchell JM, Teague CH, Kayser AS, Bartlett SE, Fields HL. Varenicline decreases alcohol consumption in heavy-drinking smokers. Psychopharmacology (Berl). 2012; 223:299–306. [PubMed: 22547331]

118. Litten RZ, Ryan ML, Fertig JB, et al. A double-blind, placebo-controlled trial assessing the efficacy of varenicline tartrate for alcohol dependence. J Addict Med. 2013; 207:277–86. [PubMed: 23728065]

119. Hutchison KE, Haughey H, Niculescu M, et al. The incentive salience of alcohol: translating the effects of genetic variant in CNR1. Arch Gen Psychiatry. 2008; 65:841–50. [PubMed: 18606956]

120. Arnone M, Maruani J, Chaperon F, et al. Selective inhibition of sucrose and ethanol intake by SR 141716, an antagonist of central cannabinoid (CB1) receptors. Psychopharmacology (Berl). 1997; 132:104–6. [PubMed: 9272766]

121. Colombo G, Agabio R, Fà M, et al. Reduction of voluntary ethanol intake in ethanol-preferring sP rats by the cannabinoid antagonist SR-141716. Alcohol Alcohol. 1998; 33:126–30. [PubMed: 9566474]

122. George DT, Herion DW, Jones CL, et al. Rimonabant (SR141716) has no effect on alcohol self-administration or endocrine measures in nontreatment-seeking heavy alcohol drinkers. Psychopharmacology (Berl). 2010; 208:37–44. [PubMed: 19902183]

123. Soyka M, Koller G, Schmidt P, et al. Cannabinoid receptor 1 blocker rimonabant (SR 141716) for treatment of alcohol dependence: results from a placebo-controlled, double-blind trial. J Clin Psychopharmacol. 2008; 28:317–24. [PubMed: 18480689]

124. Keung WM. Anti-dipsotropic isoflavones: the potential therapeutic agents for alcohol dependence. Med Res Rev. 2003; 23:669–96. [PubMed: 12939789]

125. Penetar DM, Maclean RR, McNeil JF, Lukas SE. Kudzu extract treatment does not increase the intoxicating effects of acute alcohol in human volunteers. Alcohol Clin Exp Res. 2011; 35:726–34. [PubMed: 21244439]

126. Lukas SE, Penetar D, Berko J, et al. An extract of the Chinese herbal root kudzu reduces alcohol drinking by heavy drinkers in a naturalistic setting. Alcohol Clin Exp Res. 2005; 29:756–62. [PubMed: 15897719]

127. Lukas SE, Penetar D, Zhaohui Su, et al. A standardized kudzu extract (NPI-031) reduces alcohol consumption in non-treatment-seeking male heavy drinkers. Psychopharmacology (Berl). 2013; 226:65–73. [PubMed: 23070022]

128. Penetar DM, Toto LH, Farmer SL, et al. The isoflavone puerarin reduces alcohol intake in heavy drinkers: a pilot study. Drug Alcohol Depend. 2012; 126:251–6. [PubMed: 22578529]

129. Shpilenya LS, Muzychenko AP, Gasbarrini G, Addolorato G. Metadoxine in acute alcohol intoxication: a double-blind, randomized, placebo-controlled study. Alcohol Clin Exp Res. 2002; 26:340–6. [PubMed: 11923586]

130. Pellegrini-Giampietro DE, Moroni F, Pistelli A, et al. Pyrrolidone carboxylic acid in acute and chronic alcoholism. Preclinical and clinical studies. Recenti Prog Med. 1989; 80:160–4. [PubMed: 2740606]

131. Chick J. Safety issues concerning the use of disulfiram in treating alcohol dependence. Drug Saf. 1999; 20:427–35. [PubMed: 10348093]

132. Tilg H, Day CP. Management strategies in alcoholic liver disease. Nat Clin Pract Gastroenterol Hepatol. 2007; 4:24–34. [PubMed: 17203086]

133. Leggio L, Kenna GA, Ferrulli A, et al. Preliminary findings on the use of metadoxine for the treatment of alcohol dependence and alcoholic liver disease. Hum Psychopharmacol. 2011; 26:554–9. [PubMed: 22095793]

134. Guerrini I, Gentili C, Nelli G, Guazzelli M. A follow up study on the efficacy of metadoxine in the treatment of alcohol dependence. Subst Abuse Treat Prev Policy. 2006; 1:35. [PubMed: 17176456]

135. Leggio L, Addolorato G, Cippitelli A, Jerlhag E, Kampov-Polevoy AB, Swift RM. Role of feeding-related pathways in alcohol dependence: a focus on sweet preference, NPY, and ghrelin. Alcohol Clin Exp Res. 2011; 35:194–202. [PubMed: 21058960]

136. Leggio L, Ferrulli A, Cardone S, et al. Ghrelin system in alcohol-dependent subjects: role of plasma ghrelin levels in alcohol drinking and craving. Addict Biol. 2012; 17:452–64. [PubMed: 21392177]

137. Koopmann A, von der Goltz C, Grosshans M, et al. The association of the appetitive peptide acetylated ghrelin with alcohol craving in early abstinent alcohol dependent individuals. Psychoneuroendocrinology. 2012; 37:980–6. [PubMed: 22172639]

138. Leggio L, Zywiak WH, Fricchione SR, et al. Intravenous ghrelin administration increases alcohol craving in alcohol-dependent heavy drinkers: a preliminary investigation. Biol Psychiatry. 2014; 76:734–41. [PubMed: 24775991]

139. Suchankova P, Steensland P, Fredriksson I, Engel JA, Jerlhag E. Ghrelin receptor (GHS-R1A) antagonism suppresses both alcohol consumption and the alcohol deprivation effect in rats following long-term voluntary alcohol consumption. PloS One. 2013; 8:e71284. [PubMed: 23977009]

140. Heilig M, Koob GF. A key role for corticotropin-releasing factor in alcohol dependence. Trends Neurosci. 2007; 30:399–406. [PubMed: 17629579]

141. Simms JA, Haass-Koffler CL, Bito-Onon J, Li R, Bartlett SE. Mifepristone in the central nucleus of the amygdala reduces yohimbine stress-induced reinstatement of ethanol-seeking. Neuropsychopharmacology. 2012; 37:906–18. [PubMed: 22048462]

142. Irwig MS. Decreased alcohol consumption among former male users of finasteride with persistent sexual side effects: a preliminary report. Alcohol Clin Exp Res. 2013; 37:1823–6. [PubMed: 23763349]

143. Simpson TL, Saxon AJ, Meredith CW, et al. A pilot trial of the alpha-1 adrenergic antagonist, prazosin, for alcohol dependence. Alcohol Clin Exp Res. 2009; 33:255–63. [PubMed: 18945226]

144. Fox HC, Anderson GM, Tuit K, et al. Prazosin effects on stress- and cue-induced craving and stress response in alcohol-dependent individuals: preliminary findings. Alcohol Clin Exp Res. 2012; 36:351–60. [PubMed: 21919922]

145. Thomas CP, Wallack SS, Lee S, McCarty D, Swift R. Research to practice: adoption of naltrexone in alcoholism treatment. J Subst Abuse Treat. 2003; 24:1–11. [PubMed: 12646325]