THE EUROPEAN SOCIETY OF MEDICINE
Medical Research Archives, Volume 13 Issue 2

REVIEW ARTICLE

Pharmacotherapy for Alcohol Use Disorder: A Comprehensive Review of Current Treatments and Future Directions

J. Andrew Legan MD [1], Jamie Gentry, MD [1], Jason Shugoll, M.D [1], Quincy Zhong, M.D [1], Nassima Ait-Daoud, M.D [1]

[1] University of Virginia

OPEN ACCESS

PUBLISHED
28 February 2025

CITATION
Legan, JA., Gentry, J., et al., 2025. Pharmacotherapy for Alcohol Use Disorder: A Comprehensive Review of Current Treatments and Future Directions. Medical Research Archives, [online] 13(2).
https://doi.org/10.18103/mra.v13i2.6328

DOI
https://doi.org/10.18103/mra.v13i2.6328

ISSN
2375-1924

ABSTRACT

Over the past decade, research into pharmacotherapy for alcohol use disorder (AUD) has significantly expanded. Three medications—naltrexone (including its extended-release (XR) formulation, Vivitrol®), acamprosate, and disulfiram—are Food and Drug Administration (FDA) and European Medicines Agency (EMA) approved for alcohol use disorder treatment. In some European regions, baclofen, nalmefene, and sodium oxybate are also approved for alcohol use disorder treatment. Despite their widespread use, of these medications variability in clinical outcomes underscores the need for more tailored treatment strategies.

Several emerging medications show promise for treating alcohol use disorder. Among the numerous neurotransmitter systems identified for novel drug development, the most promising compounds modulate the functions of opioids, glutamate (with or without gamma-aminobutyric acid), and serotonin. Other potential therapeutic agents target systems involved in sleep, appetite, stress response, and neuroplasticity. While more research is needed to confirm the efficacy of these agents in larger clinical trials, they represent an exciting new avenue for alcohol use disorder treatment.

In summary, while established treatments for alcohol use disorder remain essential, there is a growing need for more personalized approaches. These strategies should address not only alcohol-related reward mechanisms but also symptoms of withdrawal, cravings, depression, cognitive processing, and sleep disturbances. The exploration of new pharmacotherapies offers hope for improved outcomes, with treatment tailored to each individual's unique needs.

Introduction

Alcohol use disorder is a widespread and chronic condition marked by a compulsive inability to control alcohol consumption, even when there are severe negative consequences.

According to a 2018 report by the World Health Organization (WHO), alcohol use is associated with over 200 diseases and injury-related health conditions[1]. In 2019 alcohol was identified as the leading risk factor for disease burden among individuals aged 25 to 49, the second-leading risk factor for those aged 10 to 24, the ninth-leading risk factor across all age groups, and 2.07 million male and 374,000 female deaths in the same period[2].

Despite the severity of AUD, it remains significantly undertreated. In 2021, only about 0.9% of individuals with past-year AUD in the US received pharmacotherapy, and less than 10% of individuals with AUD in Europe receive appropriate pharmacotherapy[3,4]. Current pharmacological options approved by both the FDA and the EMA include naltrexone (oral and XR injectable forms), acamprosate, and disulfiram, while nalmefene is approved by the EMA only, and baclofen is approved in some parts of Europe. Acamprosate, which has shown efficacy in European studies, is less supported by US trials but remains an approved option in both regions. Disulfiram, an aversive agent, is only used under supervision by highly motivated patients in combination with psychosocial support.

While abstinence has been the main desired outcome in developing these earlier pharmacotherapies, total abstinence is infrequently obtained. Current research suggests that even non-abstinent recovery contributes to a reduction in alcohol-related health risks with significant socioeconomic cost benefits[5,6].

Emerging research into the pathophysiology of AUD has paved the way for novel pharmacological interventions aimed at reducing cravings, compulsive drinking, and addressing cognitive and behavioral complications associated with excessive drinking. Investigational therapies targeting neurotransmitter systems, such as opioid, glutamate, gamma-aminobutyric acid (GABA), serotonin, and dopamine, with new agents like glucagon-like-peptide-1 (GLP-1) receptor agonists, show promise for reducing cravings and supporting metabolic health. Agents that address sleep disturbances play a significant role in improving outcomes for individuals with AUD. This review examines current and emerging pharmacotherapies, highlighting their mechanisms, efficacy, and potential for personalized treatment strategies to improve care and outcomes in Europe and beyond.

Medications Influencing the Opioid System

The three main opioid receptors—mu, delta, and kappa—are inhibitory G-protein-coupled receptors, with the mu receptor playing a key role in the brain's reward system. Endogenous opioids influence habit formation and reward conditioning[7]. Positron emission tomography imaging with [11C] carfentanil shows that alcohol consumption releases endogenous opioids in the orbitofrontal cortex and nucleus accumbens (NAc), key reward areas.[8] Additionally, a greater availability of mu-opioid receptors has been significantly linked to heightened alcohol craving in individuals with alcohol use disorder[7].

Naltrexone, a mu-opioid receptor antagonist with some additional affinity for kappa and delta receptors, was approved by the FDA for AUD in 1994 based on two small clinical studies (N=174)[9,10]. Naltrexone is hypothesized to prevent relapse by reducing alcohol cue-conditioned reinforcement signals[11]. Naltrexone has been found to consistently reduce alcohol craving, drinks per drinking day, and relapse rates[12-15]. An extensive 2023 meta-analysis found the number needed to treat with oral naltrexone 50 mg daily to prevent a return to any drinking (N=2347) was 18 and to prevent return to heavy drinking (N=3170) was 11[15].

Clinical studies suggest higher doses of naltrexone (up to 150 mg daily) are safe and may improve efficacy. However, limited data exist on its effectiveness at those doses, and no direct comparisons with lower doses have been conducted[16,17]. High-dose naltrexone may still be an option for patients with AUD who experience a partial response to lower doses.

An XR formulation of naltrexone was approved by the FDA in 2006 to treat AUD[13]. Extended-release naltrexone is given as a 380 mg injection and lasts 30 days, improving compliance. A 2022 meta-analysis of seven studies comparing XR naltrexone to placebo (N=1500) found that XR naltrexone was associated with fewer drinking days and fewer heavy drinking days per month. There was no statistical difference in abstinence rates[18].

Naltrexone 300 mg daily has been associated with hepatotoxicity[19], which led to an FDA black box warning. This warning was removed in 2013 due to insufficient evidence of liver disease exacerbation[20]. A 2019 meta-analysis of 89 randomized controlled trials did not show an increased risk of any serious adverse event with naltrexone[19]. In a 2024 study of 2,940 participants with cirrhosis initiated on naltrexone, 62 had significant enzyme elevation with 30 determined to be definitively not drug induced and 32 were considered unlikely to be drug induced[20].

Nalmefene, another mu-opioid antagonist and partial agonist at the kappa receptor, is believed to bind more strongly to kappa and delta receptors than naltrexone[21,22]. Nalmefene is approved by the EMA on an as-needed basis for reducing heavy drinking. It is not approved by the FDA for the treatment of AUD[13]. One study found that nalmefene 40 mg daily was more effective than placebo in preventing heavy drinking relapse [23]; a follow-up trial (n=105) confirmed the efficacy of 20 mg and 80 mg daily[21]. However, a larger trial (n=270) found no significant reductions in heavy drinking days or cravings with nalmefene 5 mg, 20 mg, or 40 mg daily compared to placebo[24]. A 2017 meta-analysis of 1693 patients receiving nalmefene showed a statistical benefit of nalmefene over placebo for total alcohol consumption and heavy drinking days. The meta-analysis included studies where nalmefene was taken

daily and on an as-needed basis[25]. Both nalmefene and naltrexone may cause nausea, vomiting, fatigue, and precipitated withdrawal in opioid-dependent individual [22,26].

Studies have explored as-needed naltrexone for cravings. Heinälä et al. found it superior to placebo at 12 weeks with daily dosing and at 20 weeks with as-needed dosing in patients receiving cognitive coping skills training. However, no significant differences were observed in a separate group receiving supportive therapy[27]. Another study of 163 participants found no differences in average drinks per day, but targeted naltrexone significantly reduced drinks per drinking day[28].

Taken together, these studies suggest that naltrexone and nalfemene are safe and effective treatments for AUD, particularly in patients who have not yet achieved abstinence.

Medications Targeting the Glutamatergic System

1. ACAMPROSATE:

Although the exact mechanisms by which acamprosate treats AUD are not fully elucidated, it is believed to act on the glutamatergic system as a partial co-agonist at N-methyl-D-aspartic acid (NMDA) receptors. Acamprosate has been thought to restore the normal activity of glutamatergic neurotransmission in the brain by indirect inhibition of NMDA receptors and by modulation of NMDA receptors via metabotropic glutamate receptor subtype 5 antagonism. It may also affect GABA-A transmission, suggesting a role in subclinical withdrawal symptoms and potentially offering neuroprotection during withdrawal[29]. Indeed, a body of research suggests acamprosate may have neuroprotective effects through its action on the glutamatergic system and also by reducing oxidative stress and production of free radicals[30].

Acamprosate has been demonstrated to be effective in preventing alcohol relapse, with multiple systematic reviews and meta-analyses showing it improves abstinence rates, reduces heavy drinking, and alleviates withdrawal symptoms such as sleep disturbances, anxiety and general arousal[31-33]. Some studies suggest acamprosate may help offset the negative impact of baseline anxiety on alcohol recovery, and preliminary findings point to its potential as an adjunct treatment for anxiety disorders[34,35]. Treatment with acamprosate also shows lasting benefits, with reduced relapse rates and longer periods of continuous abstinence observed 3–12 months after treatment cessation[36]. Acamprosate effect on alcohol craving is not well-defined, and results from studies are mixed with the majority reporting no difference from placebo[33,37-45,47]. Acamprosate may reduce the physiological responses associated with craving (such as tachycardia), but its impact on the subjective experience of craving is less clear[46].

The COMBINE study, the largest US AUD pharmacotherapy trial (N = 1383), found that naltrexone but not acamprosate demonstrated a significant effect on drinking outcomes compared to placebo[47]. Acamprosate is most effective when initiated soon after detoxification, as delays worsen outcomes. COMBINE required 4 days of pre-trial abstinence while European trials with positive outcomes recruited participants who completed detoxification. A secondary analysis of the COMBINE trial found longer periods of pretreatment abstinence predicted a worse response to acamprosate[48]. Its use during the detoxification period is recommended based on its neuroprotective effects and efficacy in reducing withdrawal symptoms[49]. A Cochrane review of 24 randomized controlled trials (RCTs) (N = 6,915) confirmed its role in reducing relapse risk and extending abstinence[36].

The typical dose of acamprosate is 1998 mg daily for those over 60 kg and 1332 mg for those under 60 kg, though a higher dose of 3 g per day has shown increased efficacy in some studies[50]. However, a small study found that higher doses (3 g/day) may cause more nervousness compared to the standard 2 g/day dose. Overall, acamprosate is generally well tolerated, with diarrhea being the most common side effect[51]. Acamprosate is not metabolized by the liver, so its pharmacokinetics are not affected in patients with mild to moderate hepatic insufficiency and therefore safe to prescribe to patients with liver disease[52].

In summary, acamprosate is a well-supported treatment for alcohol dependence that is effective in maintaining abstinence, reducing heavy drinking in relapsing individuals, and alleviating withdrawal symptoms. Its benefits persist after treatment stops, but it is most effective when started soon after detoxification. Although its effects on craving are less consistent, acamprosate remains a valuable tool for addressing alcohol dependence, particularly in individuals with more severe alcohol use.

2. TOPIRAMATE:

Topiramate, a fructose-1,6-diphosphate analogue, was initially developed as an anti-diabetic drug but repurposed as an anti-convulsant. Topiramate works through six main mechanisms: antagonizing α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and kainate glutamate receptors, enhancing GABA-A activity at non-benzodiazepine sites, inhibiting L-type calcium channels, stabilizing voltage-dependent sodium channels, activating potassium conductance, and mildly inhibiting carbonic anhydrase[53-56]. By enhancing GABAergic inhibition, inhibiting glutamatergic excitation, and stabilizing neuronal excitability, topiramate helps balance neurotransmitter systems disrupted by chronic alcohol use and abrupt alcohol cessation[57-60].

Clinically, topiramate's effectiveness has been demonstrated in several trials. Johnson et al. showed doses up to 300 mg/day significantly improved drinking outcomes, reduced cravings, and enhanced quality of life, with a moderate effect size of 0.63[61]. Additional trials supported these findings showing topiramate's consistent efficacy, with an effect size of 0.52 and a favorable number needed to treat of 3.4. In all these trials, participants were randomized to topiramate versus placebo while actively drinking. However, two double-blind randomized controlled studies requiring pre-

treatment abstinence showed no similar benefits[62,63]. Low dose topiramate (up to 100 mg/day) in recently detoxified individuals with AUD demonstrated some efficacy in 2 clinical trials when combined with therapy[64,65].

Adverse effects associated with topiramate include cognitive impairment (eg, word-finding difficulties), paresthesias, weight loss, headache, fatigue, dizziness, and possible depression. Though some individuals find these intolerable, clinical trials have shown these effects are generally mild to moderate in intensity. Slow titration over 6-8 weeks minimizes these effects. Rare but serious ocular events (acute myopia and secondary angle-closure glaucoma) have been reported, and resolve after discontinuation[66]. Kidney stones are 2 to 4 times more common in individuals taking topiramate, likely due to an increase in urinary pH. Other serious but rare adverse events include metabolic acidosis and hypohidrosis that require closer monitoring[67].

Topiramate may also help with smoking cessation, as alcohol-dependent smokers in clinical trials showed reduced smoking rates without targeted smoking interventions[59]. Further research is needed to explore its use in patients with co-occurring bipolar disorder.

Overall, topiramate has strong evidence supporting its effectiveness as a treatment for AUD with effects on drinking not contingent on achieving pre-treatment abstinence, making it a viable option for patients unwilling or unable to attain abstinence beforehand[68]. Clinical trials have shown that topiramate reduces alcohol cravings and obsession, albeit with a smaller effect size. Additionally, topiramate improves overall well-being and quality of life while reducing the severity of AUD and its associated harmful consequences. Notably, topiramate holds promise as a dual-purpose medication: it can be used to treat alcohol withdrawal syndrome and, with continued use, prevent relapse.

Medications Modulating the GABAergic System

1. BACLOFEN

Baclofen is a GABA-B receptor agonist that has been approved for the treatment of muscle spasticity since the 1960s[69]. Baclofen is thought to treat AUD through GABA-B agonism in the mesolimbic pathway and the ventral tegmental area (VTA), which inhibits alcohol-induced dopamine release in the NAc, resulting in decreased reinforcement from alcohol consumption. Baclofen may also help with alcohol craving by reducing anxiety, as GABA-B receptors are located throughout the limbic system[70].

Baclofen became a popular treatment for AUD after the publication of the autobiography of Dr. Oliver Ameisen, a French cardiologist who claimed that high dose baclofen completely suppressed his alcohol cravings. Subsequently, several case reports, case series, and cohort studies showed promising results, which spurred the widespread use of baclofen, mainly in France[71]. France is currently the only country where baclofen has a labeled indication for AUD. This approval was granted in 2018 after years of extensive off-label use, with doses of up to 400mg daily[72].

There have been many studies and multiple meta-analyses examining the efficacy of baclofen in treating AUD with a great deal of heterogeneity between the studies and meta-analyses. There were four different meta-analyses published in 2018[69-71,73]. Bschor et al. included 14 RCTs (1,522 participants) and found a small statistically insignificant advantage of baclofen over placebo (P=0.09). In terms of specific outcomes, baclofen was no better than placebo in improving abstinence rates and was borderline statistically superior to placebo (P=0.0503) in terms of amount of drinking (ethanol consumption g/day, number of alcoholic drinks per day, and heavy drinking days per week or month)[69]. Minozzi et al. included 12 RCTs (1,128 participants) and found no superiority of baclofen over placebo in any drinking outcome (relapse at any time during the study, percent of days abstinent, percent of heavy drinking days, number of drinks per drinking day)[70]. Pierce et al. included 13 RCTs (1,492 participants) and found that baclofen was associated with increased abstinence rates (8 RCTs and 1,244 participants) and an increased time to relapse (8 RCTs and 852 participants), but not with percentage days abstinent (7 RCTs and 457 participants)[71]. A meta-analysis by Rose and Jones consisting of 12 RCTs (1,130 participants) found that baclofen had a significant effect in abstinence rates with intention-to-treat analysis (6 RCTs and 590 participants), but no effect on cumulative abstinence days or heavy drinking days[73]. There was significant overlap between the meta-analyses, with 9 RCTs included in all four[69-73]. A more recent 2024 meta-analysis by Duan et al. included 9 RCTs (670 participants) found that baclofen was superior to placebo in terms of short-term total alcohol consumption (3 RCTs and 312 participants), but not in terms of short-term heavy drinking days (6 RCTs with 503 participants) or short-term days abstinent (4 RCTs and 296 participants)[74].

Daily doses in the meta-analyses' studies ranged from 30 mg to 300 mg, which is one explanation for the variability in response across studies[69,70]. Of note, the maximum approved dose for muscle spasticity is 80 mg in most countries, including the US[69]. The meta-analysis by Pierce et al. found that lower dose baclofen actually showed better efficacy and was better tolerated[71]. Other proposed explanations for the heterogeneity include baclofen possibly having a greater effect on more severe cases of AUD and participants with co-morbid anxiety[70].

The side effect profile of baclofen includes somnolence, vertigo, headache, confusion, perspiration, muscle stiffness, abnormal movements, slurred speech, numbness and dry mouth[69,70]. A potential for tolerance to baclofen may also develop with chronic use[75,76].

Baclofen is of interest in treating alcohol use disorder (AUD) in patients with liver disease due to its minimal hepatic metabolism, and there have been clinical studies of baclofen use in AUD patients with cirrhosis.[77]. However, a 2023 meta-analysis of five studies (including RCTs and cohort studies) found no significant benefit of baclofen over placebo for maintaining abstinence in AUD patients with liver disease[78].

While there are some promising results supporting the use of baclofen in the treatment of AUD, additional studies are needed to truly determine its effectiveness. Similarly, identifying the cause of the heterogenous results across studies would also be helpful in determining the therapeutic potential of baclofen.

2. GABAPENTIN

Gabapentin, also known by its brand name Neurontin, was originally developed as an anticonvulsant and later used for neuropathic pain and restless leg syndrome. It has garnered attention as a promising off-label treatment for AUD due to its unique mechanism of action. It primarily works by modulating calcium channels at the at the alpha-2-delta type 1 (α2δ-1) site, indirectly affecting the release of neurotransmitters such as glutamate and GABA in the brain. These neurotransmitters are crucial in regulating neural excitability and play a central role in the symptoms of AUD. Evidence suggests α2δ-1 subunits of calcium channels are upregulated in the reward centers of the brain with long term alcohol use. Upon cessation of alcohol, there is a sudden drop-in GABA activity, contributing to withdrawal symptoms like anxiety, insomnia, and irritability which could be alleviated by gabapentin.

Evidence of gabapentin for the use of AUD has shown some promising but mixed results. A 16-week randomized controlled trial found that gabapentin 1200 mg total daily significantly reduced heavy drinking days and increased abstinence rates compared to placebo, confirmed by biochemical markers in 90 individuals with AUD[79]. This was further supported by a 12-week, double-blind, placebo-controlled, randomized trial that assessed gabapentin's efficacy for drinking outcomes across different doses. Gabapentin, especially at 1800 mg daily, significantly increased abstinence rates and reduced heavy drinking over 12 weeks. Abstinence rates improved with higher doses, with 17% abstinence in the 1800 mg daily group vs. 11.1% in the 900 mg daily group 4.1% in the placebo group. Gabapentin also lowered weekly heavy drinking days, cravings, depression scores, and improved sleep quality. These effects persisted at 24-week follow up, showing dose-dependent reductions in cravings and heavy drinking, suggesting gabapentin's promising role in treating AUD[80]. A smaller controlled trial showed efficacy in reducing cravings at doses as low as 300 mg twice a day[81]. However, a larger (n=346), multi-center, double-blind study which tested gabapentin enacarbil extended-release (GE-XR) 600 mg twice daily versus a placebo alongside a computerized behavioral intervention for six months, did not replicate similar results[82]. A reanalysis of the clinical trial data identified a subset of participants with higher number of heavy drinking days, lower levels of anxiety, depression and general mood disturbances and higher levels of cognitive and motor impulsivity to respond better to GE-XR[83].

One study examined the effects of combining gabapentin, up to 1200 mg daily, with naltrexone 50 mg compared to naltrexone alone. It found no significant differences in the Obsessive-Compulsive Drinking Scale total score between groups, but the naltrexone/gabapentin group exhibited greater control over drinking urges than the naltrexone-only group and had significant differences in biomarkers measurements (gamma-glutamyl transferase and % carbohydrate deficient transferrin values) indicating less heavy drinking. Sleep quality was better in the naltrexone/gabapentin group compared to others. Notably, individuals with a history of alcohol withdrawal benefited more from the naltrexone/gabapentin combination, experiencing fewer relapses to heavy drinking than those on placebo. However, this study did not compare the combination group to gabapentin as monotherapy[84].

Gabapentin is generally considered safe; however, though gabapentin is not classified as a controlled substance, it can produce euphoria and sedation at high doses, making it susceptible to misuse. Individuals with substance use disorders may be particularly vulnerable to misusing it, either alone or in combination with other substances to enhance its effects. Combining gabapentin with other depressants, especially alcohol, opioids, or benzodiazepines, may amplify its sedative effects, increasing the risk of respiratory depression, overdose, or death. Furthermore, long-term safety data for gabapentin in AUD treatment is limited, raising questions about potential dependence and withdrawal symptoms that could complicate its cessation. Given these risks, healthcare providers need to carefully monitor gabapentin use in AUD treatment, consider alternative medications when appropriate, and assess each patient's history of substance misuse to mitigate the potential for abuse.

Overall, studies for gabapentin have shown mixed results in effectiveness for the treatment of AUD. Some studies suggest it may have a role in reducing cravings, reducing days of heavy drinking and could be utilized as an augmenting agent for AUD. Gabapentin also shows some promising results when started at the time of alcohol cessation to assist in managing withdrawal symptoms. Key areas of investigation include understanding the optimal dosage, best patient populations for gabapentin, and exploring its effectiveness in combination therapies versus monotherapy.

3. PREGABALIN

Pregabalin, commonly known as its brand name Lyrica, is an anticonvulsant and neuropathic pain agent that binds to the α2δ subunit of voltage-gated calcium, similar to gabapentin. This binding inhibits excitatory neurotransmitter release, leading to decreased neuronal excitability. Its primary uses include the treatment of epilepsy and neuropathic pain, for which it has approval in both the US and Europe. Additionally, it is approved in Europe for generalized anxiety disorder, though this indication has not received approval in the U.S. Pregabalin's ability to enhance GABAergic transmission and inhibit glutamate release may help alleviate withdrawal symptoms and reduce cravings. However, there is much less data on the use of pregabalin for AUD compared to gabapentin.

A 16-week open trial of 20 patients with long-standing AUD treated with flexible doses of pregabalin (150–450

mg/day) showed that, of 15 completers, 10 remained alcohol-free while 5 relapsed. Pregabalin significantly reduced cravings, withdrawal symptoms, psychological symptoms (e.g., hostility, psychoticism), and improved liver enzyme levels[85]. In another 16-week study comparing pregabalin (up to 450 mg/day) and naltrexone (up to 50 mg/day) in 59 detoxified patients, both reduced cravings and withdrawal symptoms, but pregabalin was more effective for withdrawal with better quality of life, longer abstinence, and fewer discontinuations due to side effects[86].

While preliminary studies suggest pregabalin can reduce cravings and withdrawal symptoms and be beneficial for dual diagnosis patients, there has been a lack of large scale, randomized and placebo-controlled trials. Most studies focus on short-term outcomes, and there is a lack of data on the long-term effects and safety of pregabalin in patients with AUD. This gap limits understanding of its effectiveness in preventing relapse over extended periods.

Serotonergic Modulators

Serotonin is a monoamine neurotransmitter that regulates dopamine signaling in limbic regions and plays an important role in regulating mood. Alcohol raises serotonin levels in reward-related areas of the brain, including the NAc, VTA, amygdala, and hippocampus[87].

Serotonin 5-hydroxytryptamine-3 (5-HT3) receptors are densely located in the mesocorticolimbic system and are implicated in the regulation of dopamine release[88]. Selective 5-HT3 receptor blockade reduces alcohol consumption in animal studies[89,90]. A 2000 study by Johnson et al. (n=271) showed that ondansetron, a selective 5-HT3 receptor antagonist, was more effective than placebo at reducing alcohol consumption and increasing abstinence in patients with early onset, but not late onset alcohol use disorder[88]. Johnson et al. also identified ondansetron to be more effective in participants with certain genotypes (the LL genotype of the 5-HTTLPR serotonin transporter protein and the TT genotype of the single nucleotide polymorphism in the 3'-untranslated region of the 5-HTT gene)[91,92]. A more recent 2022 study (N= 95) of ondansetron 0.33mg BID versus placebo did not show any benefit of ondansetron in terms of drinking outcomes[93].

Serotonergic antidepressants may be helpful in treating AUD in patients with concomitant depression[87,94], but a meta-analysis of seven studies (five utilized selective serotonin receptors inhibitors, one used desipramine, and one used nefazodone and naltrexone) of patients with AUD without concomitant depression did not show any statistically significant benefit on reduction of alcohol use[95]. Improvement of alcohol use in patients with comorbid depression and AUD appears to be related to the improvement of depressive symptoms[95]. Similarly, buspirone, a 5-HT1 partial agonist, has not shown any improvement in alcohol use in patients without comorbid anxiety[94].

The antidepressant mirtazapine is of interest because of its 5-HT3 antagonism, similar to ondansetron. Mirtazapine also stimulates 5-HT1A receptors and blocks 5-HT2, 5-HT3, and α_2-noradrenergic receptors. A randomized controlled trial of 59 males with high alcohol consumption without comorbid psychiatric diagnoses utilizing mirtazapine 30mg daily did not show any benefit of mirtazapine over placebo[96].

Aripiprazole, an atypical antipsychotic, a 5-HT1A partial agonist and a 5-HT2 antagonist, was found to reduce drinks per drinking day in a 12-week randomized controlled trial of 295 participants with AUD but had no effect on abstinence. Aripiprazole was also associated with a statistically significant increase in treatment-related adverse events[97].
Overall, serotonergic antidepressants do not appear to benefit treatment of AUD, unless there are concomitant psychiatric illnesses. Ondansetron has shown mixed results with variability in terms of onset of alcohol use disorder and genetic polymorphisms. Additional studies of ondansetron would help clarify its efficacy.

Nicotinic receptor: Varenicline

Neuronal nicotinic acetylcholine receptors (nAChRs) are ligand-gated ion channels in the brain, consisting of various combinations of α and β subunits. Like other nAChR subtypes, they possess a fundamental structure of five subunits arranged around a central pore within the membrane bilayer. These receptors are widely distributed throughout the brain and are highly expressed in the mesolimbic reward circuit[98,99].

Varenicline, an FDA-approved smoking cessation aid previously marketed as Chantix®, has recently been evaluated in numerous clinical trials for its proposed benefit in AUD. Varenicline is a partial agonist of α4β2 nAChRs located in the dopamine rich VTA of the brain. Varenicline's mechanism in treating AUD likely involves reducing dopamine release in the NAc, thereby lessening alcohol's rewarding effects.

Evidence suggests that varenicline may reduce alcohol cravings and consumption, showing mixed yet promising results as a treatment for AUD[99-101]. A large trial by Litten et al. found varenicline reduced key drinking metrics regardless of smoking cessation[102], while de Bejczy et al. reported no significant effects on drinking but noted reduced cravings and phosphatidylethanol (PEth) levels[98]. Meszaros et al. found no significant effects, though results were limited by small sample size[103].

Subsequent placebo-controlled studies supported varenicline's efficacy but also examined various moderators that predicted better treatment response: reduced tobacco use, non-abstinence drinking goals, fewer years of regular drinking, and younger age[99-100][1,104]. Notably, O'Malley et al. observed greater reductions in heavy drinking among men[105], and Donato et al. found varenicline to be more effective for patients with less severe AUD[106]. These results suggest that varenicline may be most effective for patients with less severe AUD, supporting a more personalized approach to pharmacotherapy for AUD.

Varenicline is considered to have a low potential for abuse—a desired characteristic for any pharmacotherapy used in disorders with an addictive

feature. It also has 100% bioavailability regardless of concurrent food administration, few drug-drug interactions because of minimal hepatic metabolism, and a fairly rapid time to peak plasma concentrations.

Chantix, the brand name for varenicline, was discontinued by Pfizer in 2021 due to concerns for nitrosamine impurities. While Pfizer has not resumed manufacturing Chantix, generic versions of varenicline have become widely available since then. In July 2009, the FDA mandated a boxed warning on Chantix's labeling. This warning highlighted potential serious neuropsychiatric events, including changes in behavior, hostility, agitation, depressed mood, and suicidal thoughts or actions[107,108]. However, in December 2016, the FDA removed this boxed warning. This decision was informed by the Evaluating Adverse Events in a Global Smoking Cessation Study (EAGLES), a large clinical trial that assessed the neuropsychiatric safety of smoking cessation treatments, including varenicline. The study found that the risk of serious neuropsychiatric side effects with varenicline was lower than previously believed.

Together, these studies suggest that varenicline may be particularly beneficial for certain AUD subpopulations and merits further investigation, especially when integrated with behavioral support or targeted at patients with lower AUD severity.

Aversive agent: Disulfiram

Disulfiram acts by blocking the enzyme aldehyde dehydrogenase, inhibiting the oxidation of alcohol. This results in elevation of the toxic metabolite acetaldehyde causing a variety of symptoms including tachycardia, nausea, flushing, diaphoresis and dyspnea. Disulfiram was approved by the FDA and the EMA for the treatment of AUD since the 1950's and there has been mixed evidence for its efficacy over placebo in preventing use[109]. One of the major limitations is the psychological aversion being present in treatment and placebo groups, nullifying the utility in blinding[110].

A large, multicenter randomized double-blind placebo-controlled study in the 1980s (N= 605) of veterans with AUD found no significant difference in abstinence or time to first drink compared to placebo[111,112]. A randomized, open-label trial was completed in 2008 comparing efficacy of disulfiram, naltrexone, and acamprosate in treating of AUD (N=243) first with supervised medication administration followed by as-needed medication use for cravings. The study concluded that during the first phase, disulfiram improved abstinence outcomes but not in the second phase[113]. A meta-analysis in 2011 examined ten studies and found that specifically supervised disulfiram administration led to a minor reduction in number of drinking days and an increase in days until relapse when compared to placebo[114]. Several years later, Skinner et al. conducted another meta-analysis involving 22 studies to investigate the role of blinding. They concluded that blinded studies showed no statistically significant reduction in alcohol-related outcomes but confirmed that in open-label trials, supervised disulfiram was more effective than placebo. Disulfiram remained a safe treatment in these trials without significant difference between treatment and control groups in regard to serious adverse effects or hospitalizations[110]. In 2022, a systematic review was published reviewing efficacy of multiple pharmacologic interventions for AUD. The study included 156 RCTs and concluded that disulfiram did have an effect on abstinence and heavy drinking when results were stratified[109].

Overall, there is mixed evidence for the efficacy of disulfiram in treatment of AUD. The best evidence remains for medication administration under supervision. Adherence management requirement coupled with the potential of severe medical reaction limit the utility of disulfiram in the treatment of AUD. Otherwise, disulfiram is a safe alternative and can be considered in motivated patients--especially in patients with good social support who can attest to medication compliance.

Emerging Targets and Experimental Compounds

1. KETAMINE

Ketamine, an acryl-cyclo-alkylamine initially approved in the 1970s as an anesthetic by the FDA and EMA, has been explored for various uses, including AUD[115,116]. Its derivative, esketamine, was approved in 2019 by the European Commission and FDA (as Spravato nasal spray) for treatment-resistant major depressive disorder (MDD). Ketamine primarily acts as an NMDA receptor antagonist, with neuromodulatory effects on dopaminergic, opioid, and cholinergic pathways, all linked to AUD pathophysiology[117,118].

Several initial studies were conducted in the late 90's investigating the efficacy of ketamine-assisted psychotherapy in the treatment of AUD. One prospective cohort study that followed 211 patients at an addiction center either receiving ketamine-assisted psychotherapy versus standard treatment, found 65.8% achieved more than one year of abstinence compared to 24% in the control group[119]. A more recent study examined the combination of naltrexone and ketamine for AUD in patients with comorbid MDD[120]. Though the primary endpoint of the study was improvement in depressive symptomatology, the researchers found that ~80% of participants reported reduction in alcohol cravings via the obsessive-compulsive drinking scale[116,120].

In 2020, Dakwar et al. conducted a pilot study on the effects of a single ketamine infusion combined with motivational interviewing for AUD. Participants received six motivational interviewing sessions over five weeks and a single infusion of either ketamine (0.71 mg/kg) or midazolam (0.025 mg/kg). The ketamine group showed increased abstinent days, fewer heavy drinking days, and longer time to relapse[116,121]. In 2022, a double-blind placebo-controlled trial evaluated ketamine (0.8 mg/kg) combined with psychotherapy or alcohol education for AUD relapse prevention. Over three weeks, participants received weekly infusions of ketamine or saline and either psychotherapy or education. After six months, the ketamine group had a 10.1% increase in abstinent days, with the ketamine plus psychotherapy group showing the largest gain (15.9%) compared to placebo with education. No serious adverse events were reported[122].

Evidence for ketamine infusions without psychotherapy is limited. A small open-label pilot study by Terasaki et al. compared single-dose intravenous ketamine (0.5 mg/kg), intramuscular naltrexone (380 mg), or no intervention in 44 participants, using hospital readmission rates as the endpoint. No significant differences were found between groups[123]. There remains a need for larger-scale clinical trials to properly assess efficacy of treatment as well as explore optimal dosing range and frequency for treatment.

2. GLUCAGON-LIKE PEPTIDE-1 AGONISTS

Glucagon-like peptide-1 receptor agonists are another class of medication with increasing evidence for treatment of AUD. Glucagon-like peptide-1 is a hormone produced by enteroendocrine cells in the intestine. It functions predominantly to stimulate release of insulin from pancreatic β-cells, in turn lowering glucose levels, slowing gastric emptying, and promoting satiety[124,125]. Glucagon-like peptide-1 agonists are approved for treatment of diabetes and obesity in the US and Europe. These receptors are expressed in several key brain areas involved in reward and motivation including the NAc and VTA[124-127]. Though the specific mechanism remains unclear, evidence supports a modulatory role in the mesolimbic dopamine pathway. In addition to the receptor location, preclinical studies illustrated that direct stimulation of GLP-1 receptors in the VTA reduced alcohol intake in rodents[128-130]. A variation in a GLP-1 receptor gene was also linked to AUD in humans[126].

In regard to safety, initial observational studies indicated an increased risk of pancreatic pathology among patients treated with GLP-1 receptor agonists. This concern may have dissuaded earlier exploration of these medications as a treatment for AUD. Later, a systematic review and a meta-analysis discredited these findings[131].

Klause et al. conducted a 26-week randomized controlled trial with 127 AUD patients receiving either exenatide or placebo, alongside cognitive behavioral therapy. Subgroup analysis showed a ~24% reduction in heavy drinking days among obese participants (body mass index >30 kg/m², P=0.034). Functional magnetic resonance imaging analysis revealed reduced ventral striatum activity linked to addiction[132]. Wium-Anderson et al.'s register-based cohort study compared GLP-1 agonists to dipeptidyl peptidase-4 inhibitors, finding reduced alcohol intake with GLP-1 agonists during the first three months of treatment[133]. Richards et al.'s retrospective review of six AUD patients treated with semaglutide showed significant reductions in alcohol consumption, with an average AUDIT score decrease of 4.5 ± 2[134].

There remains a need for further clinical trials to better examine the efficacy and safety of GLP-1 receptor agonists for treatment of AUD.

3. OREXIN ANTAGONIST:

The hypocretin/orexin (OX) system, produced in the lateral hypothalamus, regulates motivation and stress-related behaviors, including those linked to addiction. It includes two neuropeptides, Orexin A (OX-A) and Orexin B (OX-B), and two receptors: Orexin 1 receptor (OX1R) and Orexin 2 receptor (OX2R)[135,136].

Orexin 1 receptor is more densely located in the brain regions involved in motivation whereas OX2R is located in areas associated with regulation of sleep and arousal[136]. In some structures, OXs preferentially release GABA or glutamate. There have been a small number of reports demonstrating that alcohol use upregulates ORX signaling, and that blockade of ORX signaling decreases alcohol use[137,138]. An animal research study showed the potential of OX1R antagonists, especially SB-334867, in reducing alcohol seeking without impairing cognition[139]. Another antagonist, GSK1059865, selectively decreased high levels of alcohol drinking, but had limited or no influence on moderate alcohol drinking or sucrose consumption[140]. Experiments examining the effect of OX2R antagonists are less studied, although they may not be as effective as OX1R. Some aspects of alcohol use are dependent on OX2R[141-143] so there is a potential role for a drug with dual actions on OX1R and OX2R.

Orexin system (OXS) antagonists may also reduce alcohol-seeking behavior by influencing stress pathways. Johnson et al. found that OX1R antagonists (30 mg/kg SB334867) reduced anxiety and sympathetic responses in rats, suggesting their potential for treating AUD-related anxiety and stress[144].

Suvorexant, a dual orexin receptor antagonist, has been licensed for the treatment of insomnia in the USA, Australia and Japan. A case report described a 31-year-old man with severe AUD and insomnia who, after 13 weeks of suvorexant treatment, achieved complete abstinence from alcohol, improved liver function, and resolved insomnia symptoms[145]. Additionally, clinical trials are underway to further investigate suvorexant's efficacy in treating AUD. One such trial aims to explore how suvorexant affects stress response in individuals with moderate to severe AUD[146].

There is still a need for more clinical trials to better evaluate the role of OXS antagonists in the treatment of AUD, specifically by addressing factors known to contribute to relapse, such as poor sleep and stress.

4. SODIUM OXYBATE

Sodium oxybate (SMO), also known as gamma-hydroxybutyric acid (GHB), is a short-chain fatty acid that is naturally present in brain regions like the thalamus and hypothalamus. Its use is approved for patients with AUD in Austria and Italy. It is structurally similar to the inhibitory neurotransmitter GABA, however, it acts primarily on the GHB receptor and binds to the GABA-B receptors with low affinity. It is unclear if it indirectly acts on GABA-A, though it is hypothesized that SMO can help with alcohol withdrawal though this mechanism[147]. SMO has a rapid onset (20–40 minutes) and short half-life (30–50 minutes). Its alcohol-mimicking effects are linked to dopamine increases in mesocorticolimbic circuits, which is thought to influence alcohol craving[148]. The most common side effects of SMO include nausea sedation, dizziness, and drowsiness. One of the most concerning side effects is respiratory depression, especially when combined with alcohol or other depressants.

A 2010 review of 13 trials found GHB 50 mg improved abstinence, controlled drinking, and reduced cravings and relapses at 3 months but not at 6 months [149-151]. In another trial, GHB outperformed naltrexone and disulfiram in reducing cravings but had no effect on heavy drinking[152-154]. Combining GHB with naltrexone improved abstinence but increased side effects, while adding escitalopram showed benefits at 3 and 6 months[154,155]. Statistical concerns for these trials include potential biases favoring the treatment group in open trials. A more recent network meta-regression analysis suggests SMO was more effective in high-severity populations but not in mid-severity populations, showing significant improvements both in abstinence rate and percentage of days abstinent[156].

Sodium oxybate shows potential as a treatment for alcohol use disorder, and could be particularly useful in addition to other pharmacotherapies. While preliminary evidence is promising, given the heterogeneity of SMO efficacy, further research is essential to establish its role in clinical practice.

Conclusion:

Despite significant progress in understanding the neurobiological factors that drive the development and persistence of AUD, few medications have been approved for its treatment in nearly two decades. Recently approved options, such as nalmefene in Europe and Australia and baclofen in France, highlight ongoing efforts to expand treatment options.

Among the established medications, moderate-strength evidence supports the effectiveness of 50 mg daily oral naltrexone in reducing the risk of returning to drinking, heavy drinking, and the frequency of drinking days. Acamprosate also shows moderate-strength evidence for lowering the risk of returning to any drinking and reducing the number of drinking days, though it is less effective at preventing heavy drinking. Naltrexone offers greater convenience with a single daily dose or as-needed use, while acamprosate requires three doses daily and prior alcohol detoxification. Disulfiram, though supported by limited evidence due to trial design challenges, remains an option for highly motivated individuals seeking external reinforcement to abstain, despite its risks and potential adverse effects

There is a pressing need to develop new medications that target diverse symptoms of AUD, such as withdrawal, cravings, depression, cognitive impairment, pain, and sleep disturbances, to offer a more personalized and effective approach to treatment. As our understanding of the neurobiological mechanisms underlying AUD continues to advance, so too must our commitment to expanding the arsenal of pharmacological options available. Furthermore, it is crucial to train clinicians on the latest evidence-based treatments and to actively encourage their use in clinical practice. By fostering greater awareness and confidence among healthcare providers in prescribing these medications, we can significantly improve patient outcomes and help address the underutilization of pharmacotherapy in the treatment of AUD.

Conflicts of Interest Statement: The authors declare no conflicts of interest related to this work

Funding Statement: not applicable

Acknowledgments: The authors thank the Department of Psychiatry of the University of Virginia for their support in preparing this review

References

[1] World Health Organization. *Global status report on alcohol and health 2018*. World Health Organization, 2018.

[2] Murray, Christopher J. L. , et al. "Global burden of 87 risk factors in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019." *The Lancet*, vol. 396, no. 10258, 2020, pp. 1223-1249, https://doi.org/10.1016/S0140-6736(20)30752-2.

[3] Hasin, Deborah S., et al. "Prevalence, Correlates, Disability, and Comorbidity of DSM-IV Alcohol Abuse and Dependence in the United States: Results from the National Epidemiologic Survey on Alcohol and Related Conditions." *Archives of General Psychiatry*, vol. 64, no. 7, 2007, pp. 830-842, https://doi.org/10.1001/archpsyc.64.7.830.

[4] Rehm, Jürgen, et al. "Modeling the Impact of Alcohol Dependence on Mortality Burden and the Effect of Available Treatment Interventions in the European Union." *European Neuropsychopharmacology*, vol. 23, no. 2, 2013, pp. 89-97, https://doi.org/10.1016/j.euroneuro.2012.08.001.

[5] Charlet, Katrin, and Andreas Heinz. "Harm reduction—a systematic review on effects of alcohol reduction on physical and mental symptoms." *Addiction biology* vol. 22, no. 5, 2017, pp. 1119-1159, https://doi.org/10.1111/adb.12414.

[6] Witkiewitz, Katie, James Morris, and Jalie A. Tucker. "Commentary on Henssler et al.: The Public Health Case for Promoting and Valuing Drinking Reductions in the Treatment of Alcohol Use Disorder." *Addiction*, vol. 116, no. 8, 2021, pp. 1988-1989, https://doi.org/10.1111/add.15429.

[7] Nutt, David J. "The Role of the Opioid System in Alcohol Dependence." *Journal of Psychopharmacology*, vol. 28, no. 1, 2014, pp. 8-22, https://doi.org/10.1177/0269881113504017.

[8] Mitchell, Jennifer M., et al. "Alcohol Consumption Induces Endogenous Opioid Release in the Human Orbitofrontal Cortex and Nucleus Accumbens." *Science Translational Medicine*, vol. 4, no. 116, 2012, 116ra6, https://doi.org/10.1126/scitranslmed.3002902.

[9] O'Malley, Stephanie S., et al. "Naltrexone and Coping Skills Therapy for Alcohol Dependence: A Controlled Study." *Archives of General Psychiatry*, vol. 49, no. 11, 1992, pp. 881-887, https://doi.org/10.1001/archpsyc.1992.01820110045007.

[10] Volpicelli, Joseph R., et al. "Naltrexone in the Treatment of Alcohol Dependence." *Archives of General Psychiatry*, vol. 49, no. 11, 1992, pp. 876-880, https://doi.org/10.1001/archpsyc.1992.01820110040006.

[11] Connor, Jason P., Paul S. Haber, and Wayne D. Hall. "Alcohol Use Disorders." *The Lancet*, vol. 387, no. 10022, 2016, pp. 988-998, https://doi.org/10.1016/S0140-6736(15)00122-1.

[12] Burnette, Elizabeth M., et al. "Novel Agents for the Pharmacological Treatment of Alcohol Use Disorder." *Drugs*, vol. 82, no. 3, 2022, pp. 251-274, https://doi.org/10.1007/s40265-021-01670-3.

[13] Kranzler, Henry R., and Emily E. Hartwell. "Medications for Treating Alcohol Use Disorder: A Narrative Review." *Alcohol: Clinical and Experimental Research*, vol. 47, no. 7, 2023, pp. 1224-1237, https://doi.org/10.1111/acer.15118

[14] Streeton, C., and G. Whelan. "Naltrexone, a Relapse Prevention Maintenance Treatment of Alcohol Dependence: A Meta-Analysis of Randomized Controlled Trials." *Alcohol and Alcoholism*, vol. 36, no. 6, 2001, pp. 544-552, https://doi.org/10.1093/alcalc/36.6.544.

[15] McPheeters, Melissa, et al. "Pharmacotherapy for Alcohol Use Disorder: A Systematic Review and Meta-Analysis." *JAMA*, vol. 330, no. 17, 2023, pp. 1653-1665, https://doi.org/10.1001/jama.2023.19761.

[16] Yoon, Gihyun, et al. "High-Dose Naltrexone Treatment and Gender in Alcohol Dependence." *Clinical Neuropharmacology*, vol. 39, no. 4, 2016, pp. 165-168, https://doi.org/10.1097/WNF.0000000000000152.

[17] Yoon, Gihyun, et al. "Safety, Tolerability, and Feasibility of High-Dose Naltrexone in Alcohol Dependence: An Open-Label Study." *Human Psychopharmacology: Clinical and Experimental*, vol. 26, no. 2, 2011, pp. 125-132, https://doi.org/10.1002/hup.1183.

[18] Murphy, Charles E. IV, et al. "Effect of Extended-Release Naltrexone on Alcohol Consumption: A Systematic Review and Meta-Analysis." *Addiction*, vol. 117, no. 2, 2022, pp. 271-281, https://doi.org/10.1111/add.15572.

[19] Bolton, Monica, et al. "Serious Adverse Events Reported in Placebo Randomized Controlled Trials of Oral Naltrexone: A Systematic Review and Meta-Analysis." *BMC Medicine*, vol. 17, 2019, pp. 1-13, https://doi.org/10.1186/s12916-018-1242-0.

[20] Thompson, Rachel, et al. "Safety of Naltrexone in Patients with Cirrhosis." *JHEP Reports*, vol. 6, no. 7, 2024, 101095, https://doi.org/10.1016/j.jhepr.2024.101095.

[21] Mason, Barbara J., et al. "A Double-Blind, Placebo-Controlled Study of Oral Nalmefene for Alcohol Dependence." *Archives of General Psychiatry*, vol. 56, no. 8, 1999, pp. 719-724, https://doi.org/10.1001/archpsyc.56.8.719.

[22] Swift, Robert M. "Naltrexone and Nalmefene: Any Meaningful Difference?" *Biological Psychiatry*, vol. 73, no. 8, 2013, pp. 700-701, https://doi.org/10.1016/j.biopsych.2013.03.002.

[23] Mason, Barbara J., et al. "A Double-Blind, Placebo-Controlled Pilot Study to Evaluate the Efficacy and Safety of Oral Nalmefene HCl for Alcohol Dependence." *Alcoholism: Clinical and Experimental Research*, vol. 18, no. 5, 1994, pp. 1162-1167, https://doi.org/10.1111/j.1530-0277.1994.tb00098.x.

[24] Anton, Raymond F., et al. "A Multi-Site Dose Ranging Study of Nalmefene in the Treatment of Alcohol Dependence." *Journal of Clinical Psychopharmacology*, vol. 24, no. 4, 2004, pp. 421-428, https://doi.org/10.1097/01.jcp.0000130555.63254.73.

[25] Palpacuer, Clément, et al. "Pharmacologically Controlled Drinking in the Treatment of Alcohol Dependence or Alcohol Use Disorders: A Systematic

Review with Direct and Network Meta-Analyses on Nalmefene, Naltrexone, Acamprosate, Baclofen, and Topiramate." *Addiction*, vol. 113, no. 2, 2018, pp. 220-237, https://doi.org/10.1111/add.13974.

[26] Kunzler, Nathan M., Rachel S. Wightman, and Lewis S. Nelson. "Opioid Withdrawal Precipitated by Long-Acting Antagonists." *The Journal of Emergency Medicine*, vol. 58, no. 2, 2020, pp. 245-253, https://doi.org/10.1016/j.jemermed.2019.12.015.

[27] Heinälä, Pekka, et al. "Targeted Use of Naltrexone Without Prior Detoxification in the Treatment of Alcohol Dependence: A Factorial Double-Blind, Placebo-Controlled Trial." *Journal of Clinical Psychopharmacology*, vol. 21, no. 3, 2001, pp. 287-292, https://doi.org/10.1097/00004714-200106000-00006.

[28] Kranzler, Henry R., et al. "Targeted Naltrexone for Problem Drinkers." *Journal of Clinical Psychopharmacology*, vol. 29, no. 4, 2009, pp. 350-357, https://doi.org/10.1097/JCP.0b013e3181ac5213.

[29] Kalk, Nicholas J., and A. R. Lingford-Hughes. "The Clinical Pharmacology of Acamprosate." *British Journal of Clinical Pharmacology*, vol. 77, no. 2, Feb. 2014, pp. 315-23, https://doi.org/10.1111/bcp.12070.

[30] Engelhard, Klaus, et al. "The Neuroprotective Effect of the Glutamate Antagonist Acamprosate Following Experimental Cerebral Ischemia: A Study with the Lipid Peroxidase Inhibitor U-101033e." *Anaesthesist*, vol. 49, 2000, pp. 816-21, https://doi.org/10.1007/s001010070054.

[31] Chick, Jonathan, et al. "Does Acamprosate Improve Reduction of Drinking as Well as Aiding Abstinence?" *Journal of Psychopharmacology (Oxford, England)*, vol. 17, no. 4, 2003, pp. 397-402, https://doi.org/10.1177/0269881103174017.

[32] Boeijinga, P. H., et al. "Pharmacodynamic Effects of Acamprosate on Markers of Cerebral Function in Alcohol-Dependent Subjects Administered as Pretreatment and During Alcohol Abstinence." *Neuropsychobiology*, vol. 50, 2004, pp. 71-77, https://doi.org/10.1159/000077944.

[33] Chick, Jonathan, et al. "United Kingdom Multicentre Acamprosate Study (UKMAS): A 6-Month Prospective Study of Acamprosate Versus Placebo in Preventing Relapse After Withdrawal from Alcohol." *Alcohol and Alcoholism*, vol. 35, 2000, pp. 176-187, https://doi.org/10.1093/alcalc/35.2.176.

[34] Mason, Barbara J., and Philippe Lehert. "The Effects of Current Subsyndromal Psychiatric Symptoms or Past Psychopathology on Alcohol Dependence Treatment Outcomes and Acamprosate Efficacy." *American Journal of Addiction*, vol. 19, 2010, pp. 147-154, https://doi.org/10.1111/j.1521-0391.2009.00013.x.

[35] Schwartz, Thomas L., et al."Acamprosate Calcium as Augmentation Therapy for Anxiety Disorders." *Annals of Pharmacotherapy*, vol. 44, 2010, pp. 1930-1932, https://doi.org/10.1345/aph.1P353.

[36] Rösner, Susanne, et al. "Acamprosate for Alcohol Dependence." *Cochrane Database of Systematic Reviews*, 2010, no. 9, https://doi.org/10.1002/14651858.CD004332.pub2

[37] Hammarberg, Anders, et al. "The Effect of Acamprosate on Alcohol Craving and Correlation with Hypothalamic-Pituitary-Adrenal (HPA) Axis Hormones and Beta-Endorphin." *Brain Research*, vol. 1305, suppl., 2009, pp. S2-S6, https://doi.org/10.1016/j.brainres.2009.09.093.

[38] Mason, Barbara J., et al. "Effect of Oral Acamprosate on Abstinence in Patients with Alcohol Dependence in a Double-Blind, Placebo-Controlled Trial: The Role of Patient Motivation." *Journal of Psychiatric Research,* vol. 40, 2006, pp. 383-393, https://doi.org/10.1016/j.jpsychires.2006.02.002.

[39] Morley, Kirsten, et al. "Naltrexone Versus Acamprosate in the Treatment of Alcohol Dependence: A Multi-Centre, Randomized, Double-Blind, Placebo-Controlled Trial." *Addiction*, vol. 101, 2006, pp. 1451-1462, https://doi.org/10.1111/j.1360-0443.2006.01555.x,

[40] Sass, H., et al. "Relapse Prevention by Acamprosate: Results from a Placebo-Controlled Study on Alcohol Dependence." *Archives of General Psychiatry*, vol. 53, 1996, pp. 673-680, https://doi.org/10.1001/archpsyc.1996.01830080023006.

[41] Poldrugo, F. "Acamprosate Treatment in a Long-Term Community-Based Alcohol Rehabilitation Programme." *Addiction*, vol. 92, 1997, pp. 1537-1546, https://doi.org/10.1111/j.1360-0443.1997.tb02873.x.

[42] Rubio, G., et al. "Naltrexone Versus Acamprosate: One Year Follow-Up of Alcohol Dependence Treatment." *Alcohol and Alcoholism*, vol. 36, 2001, pp. 419-425, https://doi.org/10.1093/alcalc/36.5.419.

[43] Tempesta, Enrico, et al.. "Acamprosate and Relapse Prevention in the Treatment of Alcohol Dependence: A Placebo-Controlled Study." *Alcohol and Alcoholism*, vol. 35, 2000, pp. 202-209, https://doi.org/10.1093/alcalc/35.2.202.

[44] Namkoong, Kee, et al. "Acamprosate in Korean Alcohol-Dependent Patients: A Multi-Centre, Randomized, Double-Blind, Placebo-Controlled Study." *Alcohol and Alcoholism*, vol. 38, 2003, pp. 135-141, https://doi.org/10.1093/alcalc/agg038.

[45] Richardson, Kylie, et al. "Do Acamprosate or Naltrexone Have an Effect on Daily Drinking by Reducing Craving for Alcohol?" *Addiction (Abingdon, England)*, vol. 103, no. 6, 2008, pp. 953-959, https://doi.org/10.1111/j.1360-0443.2008.02215.x.

[46] Ooteman, Wendy, et al. "The Effect of Naltrexone and Acamprosate on Cue-Induced Craving, Autonomic Nervous System and Neuroendocrine Reactions to Alcohol-Related Cues in Alcoholics." *European Neuropsychopharmacology*, vol. 17, 2007, pp. 558-566, https://doi.org/10.1016/j.euroneuro.2007.02.012.

[47] Anton, Raymond F., et al. "Combined Pharmacotherapies and Behavioral Interventions for Alcohol Dependence: The COMBINE Study: A Randomized Controlled Trial." *JAMA*, vol. 295, 2006, pp. 2003-2017, https://doi.org/10.1001/jama.295.17.2003

[48] Gueorguieva, Ralitza, et al. "Baseline Trajectories of Drinking Moderate Acamprosate and Naltrexone Effects in the COMBINE Study." *Alcoholism: Clinical and Experimental Research*, vol. 35, 2011, pp. 523-531, https://doi.org/10.1111/j.1530-0277.2010.01369.x

[49] Lingford-Hughes, A. R., et al. "Evidence-Based Guidelines for the Pharmacological Management of Substance Misuse, Addiction and Comorbidity: Recommendations from the British Association for Psychopharmacology." *Journal of Psychopharmacology*,

vol. 26, 2012, pp. 1-54, https://doi.org/10.1177/026988110401800321.

[50] Mason, Barbara J. "Acamprosate and Naltrexone Treatment for Alcohol Dependence: An Evidence-Based Risk-Benefits Assessment." *European Neuropsychopharmacology*, vol. 13, 2003, pp. 469-475, https://doi.org/10.1016/j.euroneuro.2003.08.009.

[51] Johnson, Bankole A., et al. "Dose-Ranging Kinetics and Behavioral Pharmacology of Naltrexone and Acamprosate, Both Alone and Combined, in Alcohol-Dependent Subjects." *Journal of Clinical Psychopharmacology,* vol. 23, 2003, pp. 281-293, https://doi.org/10.1097/01.jcp.0000084029.22282.bb.

[52] Coe, Christopher, et al. "Pharmacotherapy Options for Alcohol Use Disorder in Patients with Alcohol-Associated Liver Disease: A Brief Guide for Clinicians." *Clinical Liver Disease (Hoboken)*, vol. 21, no. 5, 2023, pp. 125-129, https://doi.org/10.1097/CLD.0000000000000033.

[53] White, H. Steve. "Mechanism of Action of Newer Anticonvulsants." *Journal of Clinical Psychiatry*, vol. 64, 2003, pp. 5-8.

[54] Angehagen, Mikael, et al. "Topiramate Reduces AMPA-Induced Ca(2+) Transients and Inhibits GluR1 Subunit Phosphorylation in Astrocytes from Primary Cultures." *Journal of Neurochemistry*, vol. 94, no. 4, Aug. 2005, pp. 1124-1130, https://doi.org/10.1111/j.1471-4159.2005.03259.x.

[55] Zhang, Xiao-Lei, et al. "Modulation of High-Voltage–Activated Calcium Channels in Dentate Granule Cells by Topiramate." *Epilepsia*, vol. 41, suppl. 1, 2000, pp. S52-S60, https://doi.org/10.1111/j.1528-1157.2000.tb02173.x.

[56] Dodgson, Susanna J., et al. "Topiramate as an Inhibitor of Carbonic Anhydrase Isoenzymes." *Epilepsia*, vol. 41, 2000, pp. S35-S39, https://doi.org/10.1111/j.1528-1157.2000.tb06047.x.

[57] Johnson, Bankole A. "Recent Advances in the Development of Treatments for Alcohol and Cocaine Dependence: Focus on Topiramate and Other Modulators of GABA or Glutamate Function." *CNS Drugs*, vol. 19, 2005, pp. 873-896, https://doi.org/10.2165/00023210-200519100-00005.

[58] Johnson, Bankole A. "Update on Neuropharmacological Treatments for Alcoholism: Scientific Basis and Clinical Findings." *Biochemical Pharmacology*, vol. 75, 2008, pp. 34-56, https://doi.org/10.1016/j.bcp.2007.08.005.

[59] Johnson, Bankole A., and Nassima Ait-Daoud. "Topiramate in the New Generation of Drugs: Efficacy in the Treatment of Alcoholic Patients." *Current Pharmaceutical Design*, vol. 16, 2010, pp. 2103-2112, https://doi.org/

[60] Manhapra, Ajay, et al. "Topiramate Pharmacotherapy for Alcohol Use Disorder and Other Addictions: A Narrative Review." *Journal of Addiction Medicine*, vol. 13, no. 1, Jan./Feb. 2019, pp. 7-22, https://doi.org/10.1097/ADM.0000000000000443.

[61] Johnson, Bankole A., et al. "Oral Topiramate for Treatment of Alcohol Dependence: A Randomised Controlled Trial." *The Lancet*, vol. 361, no. 9370, 2003, pp. 1677-1685, https://doi.org/10.1016/S0140-6736(03)13370-3.

[62] Likhitsathian, Surinporn, et al. "Topiramate Treatment for Alcoholic Outpatients Recently Receiving Residential Treatment Programs: A 12-Week, Randomized, Placebo-Controlled Trial." *Drug and Alcohol Dependence*, vol. 133, 2013, pp. 440-446, https://doi.org/10.1016/j.drugalcdep.2013.06.032.

[63] Kampman, Kyle M., et al. "A Double-Blind, Placebo-Controlled Trial of Topiramate for the Treatment of Comorbid Cocaine and Alcohol Dependence." *Drug and Alcohol Dependence*, vol. 133, 2013, pp. 94-99, https://doi.org/10.1016/j.drugalcdep.2013.05.026.

[64] Martinotti, Giovanni, et al. "Low-Dose Topiramate in Alcohol Dependence." *Journal of Clinical Psychopharmacology*, vol. 34, 2014, pp. 709-715, https://doi.org/10.1097/JCP.0000000000000228.

[65] Paparrigopoulos, Thomas, et al. "Treatment of Alcohol Dependence with Low-Dose Topiramate: An Open-Label Controlled Study." *BMC Psychiatry*, vol. 11, 2011, p. 41, https://doi.org/10.1186/1471-244X-11-41.

[66] Mechrgui, Monia, and Suleman Kanani. "The Ophthalmic Side Effects of Topiramate: A Review." *Cureus*, vol. 14, 2022, https://doi.org/10.7759/cureus.28513.

[67] Cerminara, Caterina, et al. "Hypohidrosis During Topiramate Treatment: A Rare and Reversible Side Effect." *Pediatric Neurology*, vol. 34, no. 5, 2006, pp. 392-94, https://doi.org/10.1016/J.PEDIATRNEUROL.2005.10.004.

[68] Maisel, Natalya C., et al. "Meta-Analysis of Naltrexone and Acamprosate for Treating Alcohol Use Disorders: When Are These Medications Most Helpful?" *Addiction*, vol. 108, 2013, pp. 275-293, https://doi.org/10.1111/j.1360-0443.2012.04054.x.

[69] Bschor, Tom, et al. "Baclofen for Alcohol Use Disorder—A Systematic Meta-Analysis." *Acta Psychiatrica Scandinavica*, vol. 138, no. 3, 2018, pp. 232-242, https://doi.org/

[70] Minozzi, Silvia, et al. "Baclofen for Alcohol Use Disorder." *The Cochrane Database of Systematic Reviews*, vol. 11, no. 11, 2018, CD012557. *Wiley Online Library*, 26 Nov. 2018, https://doi.org/10.1002/14651858.CD012557.pub2.

[71] Pierce, Mimi, et al. "Efficacy, Tolerability, and Safety of Low-Dose and High-Dose Baclofen in the Treatment of Alcohol Dependence: A Systematic Review and Meta-Analysis." *European Neuropsychopharmacology*, vol. 28, no. 7, 2018, pp. 795-806, https://doi.org/10.1016/j.euroneuro.2018.03.017.

[72] Rolland, Benjamin, et al. "Should the French Approval of Baclofen for Alcohol Dependence Be Extended to Abstinence Maintenance?" *L'Encephale*, vol. S0013-7006(24)00138-6, 6 Sept. 2024, https://doi.org/10.1016/j.encep.2024.05.001.

[73] Rose, Abigail K., and Andrew Jones. "Baclofen: Its Effectiveness in Reducing Harmful Drinking, Craving, and Negative Mood. A Meta-Analysis." *Addiction*, vol. 113, no. 8, 2018, pp. 1396-1406, https://doi.org/10.1111/add.14191.

[74] Kotake, Kazumasa, et al. "Efficacy and Safety of Alcohol Reduction Pharmacotherapy According to Treatment Duration in Patients with Alcohol Dependence or Alcohol Use Disorder: A Systematic Review and Network Meta-Analysis." *Addiction*, vol. 119, no. 5, 2024, pp. 815-832, https://doi.org/10.1111/add.16421.

[75] Chartier, Magali, et al. "Baclofen-Induced Neuro-Respiratory Toxicity in the Rat: Contribution of Tolerance and Characterization of Withdrawal Syndrome."

Toxicological Sciences, vol. 164, no. 1, 2018, pp. 153-165, https://doi.org/10.1093/toxsci/kfy073.
[76] Santos, Cynthia, and Ruben Olmedo. "Sedative-Hypnotic Drug Withdrawal Syndrome: Recognition and Treatment." *Emergency Medicine Practice*, vol. 19, no. 3 Suppl Points & Pearls, 2017, S1-S2.
[77] Leggio, Lorenzo, and Mary R. Lee. "Treatment of Alcohol Use Disorder in Patients with Alcoholic Liver Disease." *The American Journal of Medicine*, vol. 130, no. 2, 2017, pp. 124-134, https://doi.org/10.1016/j.amjmed.2016.10.004.
[78] Duan, Fangfang, et al. "Systematic Review and Meta-Analysis: Efficacy and Safety of Baclofen in Patients with Alcohol Use Disorder Co-Morbid Liver Diseases." *Journal of Psychiatric Research*, vol. 164, 2023, pp. 477-484, https://doi.org/10.1016/j.jpsychires.2023.06.042.
[79] Anton, Robert F., et al. "Efficacy of Gabapentin for the Treatment of Alcohol Use Disorder in Patients With Alcohol Withdrawal Symptoms: A Randomized Clinical Trial." *JAMA Internal Medicine*, vol. 180, no. 5, 2020, pp. 728–736, https://doi.org/10.1001/jamainternmed.2020.0249.
[80] Mason, Barbara J., et al. "Gabapentin Treatment for Alcohol Dependence: A Randomized Clinical Trial." *JAMA Internal Medicine*, vol. 174, no. 1, 2014, pp. 70-77, https://doi.org/10.1001/jamainternmed.2013.11950.
[81] Furieri, F. A., and E. M. Nakamura-Palacios. "Gabapentin Reduces Alcohol Consumption and Craving: A Randomized, Double-Blind, Placebo-Controlled Trial." *Journal of Clinical Psychiatry*, vol. 68, no. 11, 2007, pp. 1691-1700, https://doi.org/10.4088/JCP.v68n1108.
[82] Falk, Daniel E., et al. "Gabapentin Enacarbil Extended-Release for Alcohol Use Disorder: A Randomized, Double-Blind, Placebo-Controlled, Multisite Trial Assessing Efficacy and Safety." *Alcoholism: Clinical and Experimental Research*, vol. 43, no. 1, 2019, pp. 158-169, https://doi.org/10.1111/acer.13917.
[83] Laska, Eugene M., et al. "Gabapentin Enacarbil Extended-Release Versus Placebo: A Likely Responder Reanalysis of a Randomized Clinical Trial." *Alcoholism: Clinical and Experimental Research*, vol. 44, no. 9, 2020, pp. 1875-1884, https://doi.org/10.1111/acer.14414.
[84] Anton, Robert F., et al. "Gabapentin Combined With Naltrexone for the Treatment of Alcohol Dependence." *American Journal of Psychiatry*, vol. 168, no. 7, 2011, pp. 709-717, https://doi.org/10.1176/appi.ajp.2011.10101436.
[85] Guglielmo, Riccardo, et al. "Pregabalin for Alcohol Dependence: A Critical Review of the Literature." *Advances in Therapy*, vol. 29, no. 11, 2012, pp. 947-957, https://doi.org/10.1007/s12325-012-0061-5.
[86] Martinotti, Giovanni, et al. "Pregabalin Versus Naltrexone in Alcohol Dependence: A Randomised, Double-Blind, Comparison Trial." *Journal of Psychopharmacology*, vol. 24, 2010, pp. 1367-1374, https://doi.org/10.1177/0269881109102623.
[87] Ketcherside, Ariel, et al. "The Serotonin Link Between Alcohol Use and Affective Disorders." *Journal of Addiction & Prevention*, vol. 1, no. 2, 2013, p. 3.
[88] Johnson, Bankole A., et al. "Ondansetron for Reduction of Drinking Among Biologically Predisposed Alcoholic Patients: A Randomized Controlled Trial." *JAMA*, vol. 284, no. 8, 2000, pp. 963-971, https://doi.org/10.1001/jama.284.8.963.
[89] Knapp, D. J., and L. A. Pohorecky. "Zacopride, a 5-HT3 Receptor Antagonist, Reduces Voluntary Ethanol Consumption in Rats." *Pharmacology Biochemistry and Behavior*, vol. 41, no. 4, 1992, pp. 847-850, https://doi.org/10.1016/0091-3057(92)90237-a.
[90] Hodge, Clyde W., et al. "Specific Decreases in Ethanol-But Not Water-Reinforced Responding Produced by the 5-HT3 Antagonist ICS 205-930." *Alcohol*, vol. 10, no. 3, 1993, pp. 191-196, https://doi.org/10.1016/0741-8329(93)90034-L.
[91] Johnson, Bankole A., et al. "Pharmacogenetic Approach at the Serotonin Transporter Gene as a Method of Reducing the Severity of Alcohol Drinking." *American Journal of Psychiatry*, vol. 168, no. 3, 2011, pp. 265-275, https://doi.org/10.1176/appi.ajp.2010.10050755.
[92] Johnson, Bankole A., et al. "Determination of Genotype Combinations That Can Predict the Outcome of the Treatment of Alcohol Dependence Using the 5-HT3 Antagonist Ondansetron." *American Journal of Psychiatry*, vol. 170, no. 9, 2013, pp. 1020-1031, https://doi.org/10.1176/appi.ajp.2013.12091163.
[93] Seneviratne, Chamindi, et al. "A Randomized, Double-Blind, Placebo-Controlled, Pharmacogenetic Study of Ondansetron for Treating Alcohol Use Disorder." *Alcoholism: Clinical and Experimental Research*, vol. 46, no. 10, 2022, pp. 1900-1912, https://doi.org/10.1111/acer.14932.
[94] Johnson, Bankole A., and Nassima Ait-Daoud. "Neuropharmacological Treatments for Alcoholism: Scientific Basis and Clinical Findings." *Psychopharmacology*, vol. 149, 2000, pp. 327-344, https://doi.org/10.1007/s002130000371.
[95] Torrens, Marta, et al. "Efficacy of Antidepressants in Substance Use Disorders with and Without Comorbid Depression: A Systematic Review and Meta-Analysis." *Drug and Alcohol Dependence*, vol. 78, no. 1, 2005, pp. 1-22, https://doi.org/10.1016/j.drugalcdep.2004.09.004.
[96] de Bejczy, Andrea, and Bo Söderpalm. "The Effects of Mirtazapine Versus Placebo on Alcohol Consumption in Male High Consumers of Alcohol: A Randomized, Controlled Trial." *Journal of Clinical Psychopharmacology*, vol. 35, no. 1, 2015, pp. 43-50, https://doi.org/10.1097/JCP.0000000000000259.
[97] Anton, Raymond F., et al. "A Randomized, Multicenter, Double-Blind, Placebo-Controlled Study of the Efficacy and Safety of Aripiprazole for the Treatment of Alcohol Dependence." Journal of Clinical Psychopharmacology, vol. 28, no. 1, 2008, pp. 5-12, https://doi.org/10.1097/jcp.0b013e3181602fd4.
[98] de Bejczy, A., et al. "Varenicline for Treatment of Alcohol Dependence: A Randomized, Placebo-Controlled Trial." *Alcoholism: Clinical and Experimental Research*, vol. 39, no. 11, 2015, pp. 2189-2199, https://doi.org/10.1111/acer.12854.
[99] Fucito, L. M., et al. "A Preliminary Investigation of Varenicline for Heavy Drinking Smokers." *Psychopharmacology (Berl)*, vol. 215, 2011, pp. 655-663, https://doi.org/10.1007/s00213-010-2160-9.
[100] McKee, S. A., et al. "Varenicline Reduces Alcohol Self-Administration in Heavy-Drinking Smokers." *Biological Psychiatry*, vol. 66, 2009, pp. 185-190, https://doi.org/10.1016/j.biopsych.2009.01.029.
[101] Mitchell, J. M., et al. "Varenicline Decreases Alcohol Consumption in Heavy-Drinking Smokers."

Psychopharmacology (Berl), vol. 223, 2012, pp. 299-306, https://doi.org/10.1007/s00213-012-2717-x.

[102] Litten, Raye Z., et al. "Discovery, Development, and Adoption of Medications to Treat Alcohol Use Disorder: Goals for the Phases of Medications Development." *Alcoholism*: Clinical and Experimental Research, vol. 40, 2016, pp. 1368–1379, https://doi.org/10.1111/acer.13093.

[103] Meszaros, Zsuzsa S., et al. "Varenicline Treatment of Concurrent Alcohol and Nicotine Dependence in Schizophrenia: A Randomized, Placebo-Controlled Pilot Trial." *Journal of Clinical Psychopharmacology*, vol. 33, 2013, pp. 243-247, https://doi.org/10.1097/JCP.0b013e3182870551.

[104] Falk, Daniel E., et al. "Moderators of Varenicline Treatment Effects in a Double-Blind, Placebo-Controlled Trial for Alcohol Dependence: An Exploratory Analysis." *Journal of Addiction Medicine*, vol. 9, 2015, p. 296, https://doi.org/10.1097/ADM.0000000000000133.

[105] O'Malley, Stephanie S., et al. "Effect of Varenicline Combined with Medical Management on Alcohol Use Disorder with Comorbid Cigarette Smoking: A Randomized Clinical Trial." *JAMA Psychiatry*, vol. 75, 2018, pp. 129–138, https://doi.org/10.1001/jamapsychiatry.2017.3544.

[106] Donato, Suzanna, et al. "Alcohol Use Disorder Severity Moderates Clinical Response to Varenicline." *Alcoholism: Clinical and Experimental Research*, vol. 45, 2021, pp. 1877–1887, https://doi.org/10.1111/acer.14674.

[107] Doering, Paul L., and Robin Moorman Li. "Substance-Related Disorders II: Alcohol, Nicotine, and Caffeine." Pharmacotherapy: A Pathophysiologic Approach, 10th ed., edited by Joseph T. DiPiro, et al., McGraw-Hill Education, 2017, https://accesspharmacy.mhmedical.com/content.aspx?bookid=1861&sectionid=146064353.

[108] "Chantix [Package Insert]." *U.S. Food and Drug Administration*, July 2011, https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021928s025lbl.pdf. Accessed 8 Nov. 2024.

[109] Bahji, Anees, et al. "Pharmacotherapies for Adults With Alcohol Use Disorders: A Systematic Review and Network Meta-analysis." *Journal of Addiction Medicine*, vol. 16, no. 6, Nov.-Dec. 2022, pp. 630-638, https://doi.org/10.1097/ADM.0000000000000992.

[110] Skinner, Marilyn D., et al. "Disulfiram Efficacy in the Treatment of Alcohol Dependence: A Meta-analysis." *PLOS ONE*, vol. 9, no. 2, 10 Feb. 2014, e87366, https://doi.org/10.1371/journal.pone.0087366.

[111] Fuller, Robert K., et al. "Disulfiram Treatment of Alcoholism: A Veterans Administration Cooperative Study." *JAMA*, vol. 256, no. 11, 19 Sept. 1986, pp. 1449-1455, https://doi.org/10.1001/jama.1986.03380110055026.

[112] Kranzler, Henry R., and Michael Soyka. "Diagnosis and Pharmacotherapy of Alcohol Use Disorder: A Review." *JAMA*, vol. 320, no. 8, 28 Aug. 2018, pp. 815-824, https://doi.org/10.1001/jama.2018.11406.

[113] Laaksonen, Eeva, et al. "A Randomized, Multicentre, Open-Label, Comparative Trial of Disulfiram, Naltrexone and Acamprosate in the Treatment of Alcohol Dependence." *Alcohol and Alcoholism*, vol. 43, no. 1, Jan.-Feb. 2008, pp. 53-61, https://doi.org/10.1093/alcalc/agm136.

[114] Jørgensen, Carsten H., et al. "The Efficacy of Disulfiram for the Treatment of Alcohol Use Disorder." *Alcohol Clinical and Experimental Research*, vol. 35, no. 10, Oct. 2011, pp. 1749-1758, https://doi.org/10.1111/j.1530-0277.2011.01523.x.

[115] Ezquerra-Romano, Ivan, et al. "Ketamine for the Treatment of Addiction: Evidence and Potential Mechanisms." *Neuropharmacology*, vol. 142, Nov. 2018, pp. 72-82, https://doi.org/10.1016/j.neuropharm.2018.01.017.

[116] Kelson, Matthew, et al. "Ketamine Treatment for Alcohol Use Disorder: A Systematic Review." *Cureus*, vol. 15, no. 5, 3 May 2023, e38498, https://doi.org/10.7759/cureus.38498.

[117] Sleigh, Jamie, et al. "Ketamine – More Mechanisms of Action Than Just NMDA Blockade." *Trends in Anaesthesia and Critical Care*, vol. 4, no. 2-3, 2014, pp. 76-81, https://doi.org/10.1016/j.tacc.2014.03.002.

[118] Worrell, Stephen D., and Thomas J. Gould. "Therapeutic Potential of Ketamine for Alcohol Use Disorder." *Neuroscience & Biobehavioral Reviews*, vol. 126, July 2021, pp. 573-589, https://doi.org/10.1016/j.neubiorev.2021.05.006.

[119] Krupitsky, Evgeny M., and Alexander Y. Grinenko. "Ketamine Psychedelic Therapy (KPT): A Review of the Results of Ten Years of Research." *Journal of Psychoactive Drugs*, vol. 29, no. 2, Apr.-June 1997, pp. 165-183, https://doi.org/10.1080/02791072.1997.10400185.

[120] Yoon, Gihyun, et al. "Association of Combined Naltrexone and Ketamine With Depressive Symptoms in a Case Series of Patients With Depression and Alcohol Use Disorder." *JAMA Psychiatry*, vol. 76, no. 3, Mar. 2019, pp. 337-338, https://doi.org/10.1001/jamapsychiatry.2018.3990.

[121] Dakwar, Elias, et al. "A Single Ketamine Infusion Combined With Motivational Enhancement Therapy for Alcohol Use Disorder: A Randomized Midazolam-Controlled Pilot Trial." *American Journal of Psychiatry*, vol. 177, no. 2, Feb. 2020, pp. 125-133, https://doi.org/10.1176/appi.ajp.2019.19070684.

[122] Grabski, Magda, et al. "Adjunctive Ketamine With Relapse Prevention-Based Psychological Therapy in the Treatment of Alcohol Use Disorder." *American Journal of Psychiatry*, vol. 179, no. 2, Feb. 2022, pp. 152-162, https://doi.org/10.1176/appi.ajp.2021.2103027.

[123] Terasaki, Dale, et al. "Single-Dose Intravenous Ketamine or Intramuscular Naltrexone for High-Utilization Inpatients with Alcohol Use Disorder: Pilot Trial Feasibility and Readmission Rates." *Addiction Science & Clinical Practice*, vol. 17, no. 1, 22 Nov. 2022, p. 64, https://doi.org/10.1186/s13722-022-00345-y.

[124] Martinelli, Silvia, et al. "Potential Role of Glucagon-Like Peptide-1 (GLP-1) Receptor Agonists in Substance Use Disorder: A Systematic Review of Randomized Trials." *Drug and Alcohol Dependence*, vol. 264, 7 Sept. 2024, p. 112424, https://doi.org/10.1016/j.drugalcdep.2024.112424.

[125] Tufvesson-Alm, Maximilian, et al. "Insight into the Role of the Gut-Brain Axis in Alcohol-Related Responses: Emphasis on GLP-1, Amylin, and Ghrelin." *Frontiers in Psychiatry*, 9 Jan. 2023, p. 1092828, https://doi.org/10.3389/fpsyt.2022.1092828.

[126] Jerlhag, Elisabet. "GLP-1 Signaling and Alcohol-Mediated Behaviors; Preclinical and Clinical Evidence."

Neuropharmacology, vol. 136, pt. B, July 2018, pp. 343-349, https://doi.org/10.1016/j.neuropharm.2018.01.013.

[127] Jerlhag, Elisabet. "The Therapeutic Potential of Glucagon-Like Peptide-1 for Persons with Addictions Based on Findings from Preclinical and Clinical Studies." *Frontiers in Pharmacology*, 30 Mar. 2023, p. 1063033, https://doi.org/10.3389/fphar.2023.1063033.

[128] Egecioglu, Emil, et al. "The Glucagon-Like Peptide 1 Analogue Exendin-4 Attenuates Alcohol-Mediated Behaviors in Rodents." *Psychoneuroendocrinology*, vol. 38, no. 8, Aug. 2013, pp. 1259-1270, https://doi.org/10.1016/j.psyneuen.2012.11.009.

[129] Vallöf, Daniel, et al. "The Glucagon-Like Peptide 1 Receptor Agonist Liraglutide Attenuates the Reinforcing Properties of Alcohol in Rodents." *Addiction Biology*, vol. 21, no. 2, Mar. 2016, pp. 422-437, https://doi.org/10.1111/adb.12295.

[130] Vallöf, Daniel, et al. "Long-Term Treatment with a Glucagon-Like Peptide-1 Receptor Agonist Reduces Ethanol Intake in Male and Female Rats." *Translational Psychiatry*, vol. 10, no. 1, 16 July 2020, p. 238, https://doi.org/10.1038/s41398-020-00923-1.

[131] Klausen, Mette K., et al. "The Role of Glucagon-Like Peptide 1 (GLP-1) in Addictive Disorders." *British Journal of Pharmacology*, vol. 179, no. 4, Feb. 2022, pp. 625-641, https://doi.org/

[132] Klausen, Mette K., et al. "Exenatide Once Weekly for Alcohol Use Disorder Investigated in a Randomized, Placebo-Controlled Clinical Trial." *JCI Insight*, vol. 7, no. 19, 10 Oct. 2022, e159863, https://doi.org/10.1111/bph.15677.

[133] Wium-Andersen, Ida Kim, et al. "Use of GLP-1 Receptor Agonists and Subsequent Risk of Alcohol-Related Events: A Nationwide Register-Based Cohort and Self-Controlled Case Series Study." *Basic & Clinical Pharmacology & Toxicology*, vol. 131, no. 5, Nov. 2022, pp. 372-379, https://doi.org/10.1111/bcpt.13776.

[134] Richards, Jesse R., et al. "Significant Decrease in Alcohol Use Disorder Symptoms Secondary to Semaglutide Therapy for Weight Loss: A Case Series." *Journal of Clinical Psychiatry*, vol. 85, no. 1, 27 Nov. 2023, 23m15068, https://doi.org/10.4088/JCP.23m15068.

[135] Moorman, David E. "The Hypocretin/Orexin System as a Target for Excessive Motivation in Alcohol Use Disorders." *Psychopharmacology*, vol. 235, 2018, pp. 1663–1680, https://doi.org/10.1007/s00213-018-4871-2.

[136] Sakurai, T. "The Role of Orexin in Motivated Behaviours." *Nature Reviews Neuroscience*, vol. 15, 2014, pp. 719–731, https://doi.org/10.1038/nrn3837.

[137] Bayerlein, Kristina, et al. "Orexin A Expression and Promoter Methylation in Patients with Alcohol Dependence Comparing Acute and Protracted Withdrawal." *Alcohol*, vol. 45, 2011, pp. 541–547, https://doi.org/10.1016/j.alcohol.2011.02.306.

[138] Ziolkowski, M., et al. "Orexin in Patients with Alcohol Dependence Treated for Relapse Prevention: A Pilot Study." *Alcohol and Alcoholism*, vol. 51, 2016, pp. 416–421, https://doi.org/10.1093/alcalc/agv129.

[139] Lawrence, Andrew J., et al. "The Orexin System Regulates Alcohol-Seeking in Rats." *British Journal of Pharmacology*, vol. 148, 2006, pp. 752–759, https://doi.org/10.1038/sj.bjp.0706789.

[140] Lopez, Marcelo F., et al. "The Highly Selective Orexin/Hypocretin 1 Receptor Antagonist GSK1059865 Potently Reduces Ethanol Drinking in Ethanol Dependent Mice." *Brain Research*, vol. 1636, 2016, pp. 74–80, https://doi.org/10.1016/j.brainres.2016.01.049.

[141] Brown, Robyn Mary, et al. "Central Orexin (Hypocretin) 2 Receptor Antagonism Reduces Ethanol Self-Administration, but Not Cue-Conditioned Ethanol-Seeking, in Ethanol-Preferring Rats." *International Journal of Neuropsychopharmacology*, vol. 16, no. 9, 2013, pp. 2067–2079, https://doi.org/10.1017/S1461145713000333.

[142] Shoblock, James R., et al. "Selective Blockade of the Orexin-2 Receptor Attenuates Ethanol Self-Administration, Place Preference, and Reinstatement." *Psychopharmacology*, vol. 215, 2010, pp. 191–203, https://doi.org/10.1007/s00213-010-2127-x.

[143] Kastman, Hanna E., et al. "Nucleus Incertus Orexin 2 Receptors Mediate Alcohol Seeking in Rats." *Neuropharmacology*, vol. 110, Pt A, 2016, pp. 82–91, https://doi.org/10.1016/j.neuropharm.2016.07.006.

[144] Johnson, Philip L., et al. "Activation of the Orexin 1 Receptor Is a Critical Component of CO2-Mediated Anxiety and Hypertension but Not Bradycardia." *Neuropsychopharmacology*, vol. 37, no. 8, 2012, pp. 1911–1922, https://doi.org/10.1038/npp.2012.38.

[145] Campbell, Erin J., et al. "The Dual Orexin Receptor Antagonist Suvorexant in Alcohol Use Disorder and Comorbid Insomnia: A Case Report." *Clinical Case Reports*, vol. 12, no. 5, 2024, e8740, https://doi.org/10.1002/ccr3.8740.

[146] Stephanie M Gorka. "Orexin Receptor Antagonists as Modulators of Threat Sensitivity in Individuals With Alcohol Use Disorder." ClinicalTrials.gov identifier: NCT05656534. Updated Sept 19, 2024. Accessed Nov 22, 2024. https://clinicaltrials.gov/study/NCT05656534.

[147] Caputo, Fabio, et al. "Gamma Hydroxybutyric Acid (GHB) for the Treatment of Alcohol Dependence: A Review." *International Journal of Environmental Research and Public Health*, vol. 6, no. 6, 2009, pp. 1917–1929, https://doi.org/10.3390/ijerph6061917.

[148] Snead, O. Carter III, and K. Michael Gibson. "Gamma-Hydroxybutyric Acid." *New England Journal of Medicine*, vol. 352, 2005, pp. 2721–2732, https://doi.org/10.1056/NEJMra044047.

[149] Leone, Maurizio A., et al. "Gamma-Hydroxybutyrate (GHB) for Treatment of Alcohol Withdrawal and Prevention of Relapses." *Cochrane Database of Systematic Reviews*, 2010, Issue 2, Art. No.: CD006266, https://doi.org/10.1002/14651858.CD006266.pub2.

[150] Di Bello, M. G., et al. "Gamma-Hydroxybutyric Acid Induced Suppression and Prevention of Alcohol Withdrawal Syndrome and Relief of Craving in Alcohol Dependent Patients." *Alcologia*, vol. 7, no. 2, 1995, pp. 111-118

[151] Gallimberti, L., et al. "Gamma-Hydroxybutyric Acid in the Treatment of Alcohol Dependence: A Double-Blind Study." *Alcoholism: Clinical and Experimental Research*, vol. 16, 1992, pp. 673-676, https://doi.org/10.1111/j.1530-0277.1992.tb00658.x.

[152] Nava, Felice, et al. "Comparing Treatments of Alcoholism on Craving and Biochemical Measures of Alcohol Consumption." *Journal of Psychoactive Drugs*, vol.

38, no. 3, 2006, pp. 211–217, https://doi.org/10.1080/02791072.2006.10399846.
[153] Caputo, Fabio, et al. "Gamma-Hydroxybutyric Acid versus Naltrexone in Maintaining Alcohol Abstinence: An Open Randomized Comparative Study." *Drug and Alcohol Dependence*, vol. 70, 2003, pp. 85–91, https://doi.org/10.1016/s0376-8716(02)00340-x.
[154] Caputo, Fabio, et al. "Comparing and Combining Gamma-Hydroxybutyric Acid (GHB) and Naltrexone in Maintaining Abstinence from Alcohol: An Open Randomised Comparative Study." *European Neuropsychopharmacology*, vol. 17, no. 12, 2007, pp. 781–789, https://doi.org/10.1016/j.euroneuro.2007.04.008.
[155] Stella, Luigi, et al. "An Open Randomized Study of the Treatment of Escitalopram Alone and Combined with Gamma-Hydroxybutyric Acid and Naltrexone in Alcoholic Patients." *Pharmacological Research*, vol. 57, 2008, pp. 312–317, https://doi.org/10.1016/j.phrs.2008.03.001.
[156] Guiraud, Julien, et al. "Sodium Oxybate for Alcohol Dependence: A Network Meta-Regression Analysis Considering Population Severity at Baseline and Treatment Duration." *Alcohol and Alcoholism*, vol. 58, no. 2, 2023, pp. 125–133, https://doi.org/10.1093/alcalc/agac070.