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Review Article

# Pharmacological Approaches in Alcohol Use Disorder-Exploring Off-Label an Emerging Treatments in Clinical and Preclinical Evidence

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**ABSTRACT**

Alcohol Use Disorder (AUD) presents a significant challenge, with limited efficacy and adherence to current FDA-approved treatments. This comprehensive review analyzes the spectrum of pharmacological management for AUD. To examine the efficacy, mechanisms, and therapeutic potential of various drug classes, including metabolic, anticonvulsants, antihypertensives, neuroprotective agents, antibiotics, in the management of AUD. The review identified promising interventions across various drug classes, including PPAR agonists, anticonvulsants, GABAergic drugs, antihypertensives, neuroprotective agents, cognitive enhancers, and tetracycline antibiotics. However, the efficacy of these interventions varied, and individual responses were often heterogeneous. Future research should focus on understanding individual variations in treatment responses and developing personalized approaches. The integration of pharmacological management, supported by clinical and preclinical evidence, may provide the most effective path forward in AUD management.

**Keywords:** Alcohol Use disorder, AUD, Off-Label AUD treatment, Alcohol dependance.

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## INTRODUCTION

Alcohol Use Disorder (AUD) is a condition marked by the inability to control alcohol consumption despite negative consequences. Also known as alcoholism or alcohol dependence, it is commonly treated with behavioural therapy, medications, support groups, and detoxification. Pharmacological treatments are often preferred as they directly address the neurochemical imbalances caused by alcohol dependence (Yang *et al*., 2022). The treatment options for Alcohol Use Disorder (AUD) are limited, with only three FDA-approved drugs: naltrexone, acamprosate, and disulfiram. Each of these has notable clinical limitations. Naltrexone helps reduce heavy drinking days, while acamprosate is effective in maintaining abstinence (Haque and Leggio, 2024), suffers from poor bioavailability and demanding dosing schedules, impacting adherence. Naltrexone is effective in reducing heavy drinking days (Anton, 2008), and Acamprosate is effective in maintaining abstinence but with poor bioavailability (~11%) and demands 3 doses per day (Tolomeo and Baldacchino, 2021), which will have a significant impact on medication adherence. Disulfiram operates through an aversive mechanism by inhibiting aldehyde dehydrogenase, but its efficacy is severely limited by poor patient compliance and potential adverse drug reactions (Lanz *et al*., 2023). Most of the meta-analysis reports indicate that these medications are statistically superior to placebo, achieving 10-15% compared to placebo, but relapse rates are alarmingly high, ranging across 60-90% in various studies despite psychosocial support (Del Re *et al*., 2013). This limited efficacy profile, coupled with significant heterogeneity in treatment response and high relapse rates, underscores the critical need for expanding the therapeutic armamentarium for AUD treatment. Drug repurposing emerges as a strategic approach, leveraging well-established safety profiles and targeting known pathways involved in AUD. In both clinical and preclinical studies, different types of drugs, such as metabolic, anticonvulsants, GABAergic, antihypertensive, neuroprotective agents, cognitive enhancers, antipsychotics, and tetracycline antibiotics, have shown promise in lowering alcohol use and improving symptoms related to alcoholism. This review looks at the current limitations of FDA-approved drugs, the effectiveness of different pharmacological interventions in treating AUD, and the benefits of repurposing drugs. It stresses how important it is to try a lot of different treatment options for this complicated disorder. The rationale for this comprehensive review is to analyze the spectrum of pharmacological management for AUD,

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synthesizing evidence. Explore the effectiveness of different drug classes and repurposed medications for managing AUD.

## PHARMACOLOGICAL MANAGEMENT

### Metabolic drugs on AUD

#### *Pioglitazone (PIO)*

Several studies have investigated the effects of PIO on AUD in animal models and humans. PIO treatment in ethanol-fed C57BL/6J mice decreased mitochondrial superoxide and HIF-1α mRNA levels in Alveolar Macrophages (AMs), suggesting a reduction in oxidative stress (Crotty *et al.*, 2024), while improving glucose and glutamine oxidation. PIO Modulated the Rostromedial Tegmental nucleus (RMTg), Central Amygdala (CeA), and Ventral Tegmental Area (VTA), significantly reducing alcohol cravings in msP rats (Fotio *et al.*, 2021). PIO, when combined with naltrexone, reduced both alcohol consumption and relapse in msP rats (Stopponi *et al.*, 2013). It also reduces elevated levels of IL-1β and TNF-α mRNA in neonatal C57BL/6 mice, blocking microglial activation and immune response, which may contribute to its effects on AUD (Drew *et al.*, 2015). In human studies, PIO administration resulted in a reduction in audit scores, reflecting decreased alcohol consumption before and after treatment (Dieperink *et al.*, 2021). However, in another study, results were contrasting, where the PIO group experienced increased cravings for alcohol, along with higher anxiety and depressive moods compared to the placebo group (Schwandt *et al.*, 2020).

### Fenofibrate

Fenofibrate found no significant difference in alcohol craving or consumption between the fenofibrate and placebo groups in human trials (Mason *et al.*, 2024). In contrast, animal studies have shown more promising outcomes. Fenofibrate brought GLT-1 levels back to normal in male Sprague-Dawley rats, fixed the tone of glutamatergic cells, and lowered GFAP and pIκBα levels, which showed that astrogliosis and NF-κB activation were reversed. This led to a reduction in ethanol consumption (Villavicencio-Tejo *et al.*, 2021). In the same way, it stopped rats from associating ethanol with enjoyable or rewarding effects, which decreased their alcohol use both immediately and over time through changes in their behaviour (Rivera-Meza *et al.*, 2017). The treatment led to a reduction of ethanol intake by up to 70% within a day, and even up to 90% in the dark phase. The quick change of ethanol to acetaldehyde and a big rise in liver catalase enzyme activity were responsible for this drop. These studies suggest fenofibrate may have the potential to modulate alcohol consumption, though further investigation is needed to clarify its effects (Karahanian *et al.*, 2014).

### Lorcaserin

Lorcaserin was investigated for its effects on AUD and found that lorcaserin reduced both alcohol intake and cravings. Additionally, the treatment led to a significant improvement in psychological health. These findings suggest that lorcaserin may have a beneficial impact on managing alcohol consumption and associated psychological symptoms (Campbell *et al.*, 2021).

### Exenatide

Recent studies have explored the potential of GLP-1 receptor agonists in addressing AUD. Preliminary findings indicate its impact on neurochemical pathways linked to addiction, particularly dopamine regulation. This reduction was associated with a significant decrease in both heavy drinking days and total alcohol consumption. These results suggest that exenatide may help reduce alcohol intake in this patient population. Further research is needed to explore its potential as a treatment for AUD (Klausen *et al.*, 2022).

### Metformin

Metformin was investigated in Wistar male rats and found that it reduced oxidative stress in both the frontal lobe and hippocampus. The study also showed that metformin increased neuroglobin expression in the frontal cortex. Additionally, metformin exhibited antioxidant and anxiolytic effects, suggesting potential neuroprotective benefits. These findings highlight metformin's possible role in reducing oxidative damage and promoting mental well-being (Bonea *et al.*, 2020).

### Semaglutide

Semaglutide on alcohol consumption in both male and female mice and rats. In naïve rats, it enhanced GABA activity, suggesting a potential mechanism for its effects on alcohol use. However, this enhancement was not observed in dependent rats, indicating that dependence may alter semaglutide's action. In mice, semaglutide reduced alcohol consumption in a dose-dependent manner, demonstrating its potential to modulate drinking behaviour (Chuong *et al.*, 2023).

### Anticonvulsants and GABAergic Drugs on AUD

#### *Topiramate*

Several studies have explored the effects of topiramate on alcohol consumption and related symptoms. Topiramate reduced alcohol preference in C57BL/6J mice, though the difference was not statistically significant (Farook *et al.*, 2009). When it is used as an adjuvant therapy to psychotherapeutic treatment in humans, topiramate significantly reduces depression, anxiety, and alcohol cravings (Paparrigopoulos *et al.*, 2011). In another study, topiramate significantly reduced alcohol cravings compared to naltrexone, with reductions in both BMI and GGT levels in the topiramate group. These studies highlight topiramate's potential

for managing AUD, particularly in reducing cravings and improving mood (Morley *et al.*, 2024).

## Divalproex sodium

Divalproex sodium in patients undergoing acute alcohol withdrawal. The study found that the divalproex sodium group used significantly less oxazepam compared to the placebo group, suggesting a reduced need for benzodiazepines. This indicates that divalproex sodium may help alleviate withdrawal symptoms and potentially slow the progression of acute alcohol withdrawal. The results support its use as an adjunctive treatment in managing alcohol withdrawal, reducing the reliance on traditional benzodiazepines (Reoux *et al.*, 2001).

## Gabapentin

Gabapentin was investigated on alcohol consumption and found that the gabapentin group showed significant improvement compared to the placebo group. The study demonstrated that gabapentin helped reduce alcohol consumption in participants, suggesting its potential as an effective treatment for AUD. These findings support the use of gabapentin as a pharmacological intervention for managing alcohol consumption. The results highlight gabapentin's possible role in addressing alcohol cravings and withdrawal symptoms (Furieri and Nakamura-Palacios, 2007).

## Pregabalin

The effects of pregabalin on Alcohol Withdrawal Symptoms (AWS) and cravings for alcohol. The study found that alcohol withdrawal symptoms and cravings significantly decreased over time in patients treated with pregabalin. These improvements were observed compared to the placebo group, suggesting that pregabalin is both effective and safe for managing mild-to-moderate alcohol withdrawal symptoms (Di Nicola *et al.*, 2010).

## Baclofen

The investigation on the effects of baclofen in AUD found that it showed the potential to reduce drinking behaviors. The study indicated that a dosage of 90 mg/day was slightly more effective for men, while 30 mg/day was better tolerated by women. This suggests that both dose and sex may play a role in baclofen's efficacy and tolerability. The results highlight the importance of personalized treatment strategies when using baclofen for AUD (Garbutt *et al.*, 2021). Despite debates on the efficacy of baclofen for AUD, it is considered a promising treatment for moderate to severe cases, particularly in European countries and Australia (de Beaurepaire *et al.*, 2019).

## Antihypertensive and Cardiovascular Drugs on AUD

### *Propranolol*

In the comparison between placebo and propranolol, Propranolol was associated with a notable reduction in alcohol cravings compared to the placebo group. This decrease in subjective craving underscores its potential effectiveness in managing alcohol-related urges, positioning it as a promising treatment option for craving reduction (Lonergan *et al.*, 2016).

## Prazosin

Prazosin was observed to have a significant interaction between treatment condition and time, with participants in the prazosin group showing a more substantial decrease in both the number of drinks and the number of heavy drinking days compared to those in the placebo group. The prazosin group demonstrated a greater reduction in drinking rates and the likelihood of heavy drinking over time. However, participants in the prazosin group were more likely to experience side effects such as drowsiness and edema compared to the placebo group (Simpson *et al.*, 2018).

## Doxazosin

Doxazosin may reduce alcohol consumption in individuals with a high Family History Density of Alcoholism (FHDA). However, no significant differences were observed between the doxazosin and placebo groups when considering the entire sample. This indicates that doxazosin's effectiveness might be selective, depending on the presence of a strong family history of alcoholism (Kenna *et al.*, 2016). Additionally, doxazosin reduces alcohol intake in male alcohol-preferring (P) rats, supporting the involvement of the noradrenergic system in alcohol consumption and suggesting that it could be a promising once-daily treatment option for AUDs (O'Neil *et al.*, 2013).

## Spironolactone

Patients treated with spironolactone showed a greater reduction in weekly alcohol intake compared to those who did not receive the drug. This difference represented an additional decrease in alcohol use among the spironolactone group. Among participants who initially consumed more than seven drinks per week, those on spironolactone showed a greater reduction in drinking compared to controls. Notably, there was no significant difference in drinking reduction among participants with lower baseline alcohol use. Additionally, an important dose-response relationship was identified, with higher doses of spironolactone correlating with more substantial reductions in alcohol consumption (Palzes *et al.*, 2021).

## Neuroprotective and Cognitive Enhancers on AUD

### *N-acetylcysteine (NAC)*

Chronic alcohol exposure leads to overactive glutamate signalling, contributing to cravings and relapse. NAC restores glutamate homeostasis by increasing extracellular glutamate through the cystine-glutamate antiporter. This reduces the overactivation of glutamatergic signalling and its impact on alcohol consumption in individuals with Cannabis Use Disorder (CUD). Participants in the NAC group were more likely to remain abstinent from

alcohol between visits, consumed fewer drinks per week, and reported fewer drinking days compared to those in the placebo group. Notably, the amount of cannabis use did not correlate with any changes in alcohol consumption patterns (Squeglia *et al.*, 2018). In another trial, NAC was associated with a significant reduction in the quantity of alcohol consumed per drinking day compared to a placebo. However, the study did not find significant differences in secondary outcomes, including the frequency of heavy drinking days or the rates of abstinence from alcohol (Morley *et al.*, 2023).

## Ketamine

Ketamine acts as a non-competitive NMDA receptor antagonist, temporarily dampening glutamate signalling in a study Ketamine administration in combination with memory retrieval led to a notable reduction in participants' subjective urges to drink, with significant decreases in the desire to consume alcohol both before and after consumption, in comparison to control groups. Additionally, the retrieval + ketamine group experienced a marked reduction in alcohol consumption, measured over a period following the intervention. These effects were sustained over an extended follow-up, during which participants continued to show significant reductions in their weekly alcohol consumption (Das *et al.*, 2019).

## Memantine

NMDA receptor antagonist memantine was evaluated on alcohol craving and its dissociative effects. The results indicated that pretreatment with memantine significantly reduced alcohol craving before alcohol consumption. However, no effect was observed on craving after alcohol administration. Additionally, memantine was found to enhance the dissociative effects of alcohol without influencing its sedative, stimulant, or overall intoxicating properties (Bisaga and Evans, 2004). In contrast, another study of memantine in individuals with AUD indicated that it did not produce a significantly better outcome than placebo. Memantine showed slightly worse results compared to the placebo in terms of its effectiveness on AUD. This suggests that memantine may not provide substantial benefits over placebo in the treatment of AUD (Evans *et al.*, 2007).

## Omega-3 fatty acids

Omega-3 fatty acids on alcohol consumption in individuals with AUD found that omega-3 fatty acids led to a significant reduction in the number of days alcohol was consumed. However, no significant differences were observed in other alcohol consumption parameters or relapse rates (Pauluci *et al.*, 2022).

## Probiotic supplementation

The impact of probiotic supplementation on anxiety and depression in patients with Alcohol Dependence Syndrome (ADS) found that probiotic treatment led to a significant reduction in both anxiety and depression levels. Notably, after three months, the probiotic group exhibited a more substantial improvement in anxiety severity than the non-probiotic group, highlighting the potential of probiotics in alleviating these psychological symptoms in ADS patients (Panati *et al.*, 2024).

## Tetracycline antibiotics on AUD

Tetracycline antibiotics are known to have anti-inflammatory properties, including the ability to reduce neuroinflammation. Animal studies demonstrated ethanol consumption in C57BL/6J mice, administering minocycline with a single daily dose of 50 mg/kg. Their findings revealed that minocycline significantly reduced ethanol intake in both male and female mice, with reductions consistently observed across different treatment phases. Notably, the effects were reversible, as ethanol consumption returned to baseline levels following the cessation of minocycline. Additionally, the reduction was reproducible with subsequent treatments, suggesting that the mice did not develop tolerance to minocycline's effects on alcohol consumption (Agrawal *et al.*, 2011) followed by another study investigated the effects of three tetracycline derivatives-doxycycline, minocycline, and tigecycline-on binge-like alcohol consumption using male and female C57BL/6J (B6) mice in the High Drinking in the Dark (HDID) model. The study demonstrated that all three compounds effectively reduced alcohol intake and blood alcohol levels in both sexes. Among the derivatives, tigecycline exhibited consistent efficacy across multiple doses, suggesting a broader dose-response effect. In contrast, doxycycline and minocycline showed significant reductions in alcohol intake only at higher doses. Additionally, the study observed changes in water and saccharin intake with doxycycline and minocycline, suggesting that these tetracycline derivatives may influence general fluid consumption behaviors beyond alcohol-specific effects, though the mechanisms remain to be elucidated (Crabbe *et al.*, 2020).

## Other therapeutic agents on AUD

### *Varenicline*

Varenicline is a partial agonist at the α4β2 nicotinic acetylcholine receptors and a full agonist at the α7 nicotinic acetylcholine receptors. It is primarily used as a smoking cessation aid to help individuals quit smoking by reducing cravings and withdrawal symptoms. A study conducted on heavy-drinking smokers found that varenicline significantly lowered alcohol intake and supported abstinence more effectively than placebo. Following an initial alcohol dose, participants on varenicline experienced reduced cravings and decreased subjective enjoyment and intoxication levels associated with drinking. The medication was generally well tolerated, with few adverse effects, and its combination with alcohol did not notably alter physiological responses or cause nausea (McKee *et al.*, 2009).

### Ondansetron

The 5-$HT_3$ receptors play a role in this process by enhancing dopamine release in response to alcohol. By blocking these receptors, ondansetron reduces the dopamine surge, decreasing the rewarding effects of alcohol (Engleman *et al.*, 2008). Clinical research between ondansetron and placebo uncovered that ondansetron effectively reduced alcohol consumption in individuals with early-onset alcoholism. Treatment with ondansetron, especially at a moderate dosage, resulted in a reduction in the number of drinks consumed daily and on drinking days, compared to a placebo group. Moreover, ondansetron improved the likelihood of abstinence, with participants experiencing more alcohol-free days and extended periods of sobriety. The drug also contributed to a decrease in plasma Carbohydrate-Deficient Transferrin (CDT) levels, an important biomarker for alcohol consumption, providing further evidence of its effectiveness in curbing alcohol intake. These findings suggest that ondansetron may be a promising treatment option for early-onset alcoholism, likely by addressing serotonergic imbalances (Johnson *et al.*, 2000).

### Mifepristone

Mifepristone blocks glucocorticoid receptors, reducing the effects of excess cortisol. Normalizing the HPA axis helps decrease stress-induced alcohol cravings and consumption. It was found to reduce alcohol intake in alcohol-dependent rats when administered both systemically and via direct injection into the central amygdala. The reduction in alcohol consumption was dose-dependent and specific to the dependent rats, highlighting the targeted effect of mifepristone on alcohol dependence rather than on non-dependent rats. Additionally, a human laboratory model demonstrated that mifepristone significantly decreased alcohol craving and the number of alcoholic drinks consumed per week in alcohol-dependent individuals following 7 days of treatment (Vendruscolo *et al.*, 2015).

### Ibudilast

Ibudilast inhibits multiple isoforms of Phosphodiesterases (PDEs), especially PDE4, which is implicated in inflammation and neuroplasticity. By inhibiting PDE4, ibudilast increases intracellular levels of cAMP, leading to downstream effects on neurotransmitter systems involved in reward and addiction. In a preclinical study, Ibudilast reduces alcohol consumption in various models of alcohol dependence. In both rat and mouse studies, ibudilast significantly decreased ethanol intake, with about a 50% reduction observed in rats during the maintenance and relapse phases. In Ethanol-dependent (EtOH) C57BL/6J mice, ibudilast effectively lowered drinking levels to those of non-dependent control mice, particularly at higher doses. The reduction was most pronounced during the initial administration but diminished over time. These findings suggest that ibudilast targets mechanisms specific to alcohol dependence rather than simply suppressing general ingestive behaviour (Bell *et al.*, 2015).

### Advantages of Drug Repurposing

Many antipsychotic drugs, including amisulpride, aripiprazole, flupenthixol decanoate, olanzapine, quetiapine, and tiapride, have been explored for repurposing in treating AUD, as demonstrated in a meta-analysis of 13 double-blind trials; however, none significantly outperformed placebo in preventing relapse, reducing heavy drinking, cravings, or delaying the first drink, though placebo showed greater effectiveness in increasing abstinent days and reducing drinking (Kishi *et al.*, 2013). This underscores the importance of repurposing and exploring other drugs, leveraging the well-established safety profiles of existing medications, derived from extensive clinical use and supported by robust adverse event databases. This foundation significantly facilitates clinical implementation by reducing the risk associated with unknown side effects. Additionally, repurposing leverages drugs that target established pathways relevant to AUD, such as GABAergic, dopaminergic, and glutamatergic systems, which play pivotal roles in alcohol craving, withdrawal, and relapse (Dharavath *et al.*, 2023). Drugs like naltrexone and acamprosate target opioid and glutamate pathways, and repurposed drugs with similar mechanisms can synergistically modulate these circuits, thereby reducing alcohol-seeking behaviors and supporting recovery. Neuroinflammation, strongly associated with AUD pathophysiology, is another key target in repurposing strategies. Many repurposed drugs, such as those that function as NMDA receptor antagonists, effectively reduce pro-inflammatory cytokines, offering both anti-inflammatory and neuroprotective effects that mitigate AUD-related neural damage (Clapp *et al.*, 2014). Moreover, certain repurposed drugs improve mitochondrial function, addressing oxidative stress and enhancing neural resilience against alcohol-induced damage (Haorah *et al.*, 2008). Cost is another compelling factor in drug repurposing: developing new drugs is financially burdensome and time-intensive, whereas repurposing leverages existing drugs with established manufacturing and distribution channels. This significantly reduces both research and development costs, making AUD treatments more accessible and cost-effective for healthcare systems.

## CONCLUSION

The evidence suggests that while many interventions show promise, their efficacy varies significantly among individuals. Future research should focus on understanding these variations and developing personalized treatment approaches. The integration of pharmacological treatments, supported by both clinical and preclinical evidence, offers the most promising path forward in AUD treatment. By exploring these diverse therapeutic avenues and fostering a collaborative effort across scientific, medical, and policy domains, we can pave the way for

more effective and accessible treatments for individuals battling AUD, ultimately improving their chances of recovery and quality of life.

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## CONFLICT OF INTEREST

The authors declare that there is no conflict of Interest.

## ABBREVIATIONS

**AUD:** Alcohol Use Disorder; **FDA:** Food and Drug Administration; **PPAR:** Peroxisome Proliferator-Activated Receptor; **GABAergic:** Gamma-Aminobutyric Acid-ergic; **PIO:** Pioglitazone; **AMs:** Alveolar Macrophages; **HIF-1α:** Hypoxia-Inducible Factor 1-alpha; **RMTg:** Rostromedial Tegmental nucleus; **CeA:** Central Amygdala; **VTA:** Ventral Tegmental Area; **IL-1β:** Interleukin-1 beta; **TNF-α:** Tumor Necrosis Factor-alpha; **GLT-1:** Glutamate transporter 1; **GFAP:** Glial Fibrillary Acidic Protein; **pIκBα:** Phosphorylated Inhibitor of Kappa B alpha; **GLP-1:** Glucagon-Like Peptide-1; **AWS:** Alcohol Withdrawal Symptoms; **FHDA:** Family History Density of Alcoholism; **msP rats:** Marchigian Sardinian alcohol-preferring rats; **NAC:** N-acetylcysteine; **CUD:** Cannabis Use Disorder; **NMDA:** N-Methyl-D-aspartate; **CDT:** Carbohydrate-Deficient Transferrin; **HPA axis:** Hypothalamic-Pituitary-Adrenal axis; **PDEs:** Phosphodiesterases; **PDE4:** Phosphodiesterase 4; **cAMP:** cyclic Adenosine Monophosphate; **EtOH:** Ethanol-dependent; **ADS:** Alcohol Dependence Syndrome; **HDID:** High Drinking in the Dark.

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