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REVIEW ARTICLE

Novel Agents for the Pharmacological Treatment of Alcohol Use Disorder

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Abstract

Alcohol use disorder (AUD) is a highly prevalent but severely under-treated disorder, with only three widely-approved pharmacotherapies. Given that AUD is a very heterogeneous disorder, it is unlikely that one single medication will be effective for all individuals with an AUD. As such, there is a need to develop new, more effective, and diverse pharmacological treatment options for AUD with the hopes of increasing utilization and improving care. In this qualitative literature review, we discuss the efficacy, mechanism of action, and tolerability of approved, repurposed, and novel pharmacotherapies for the treatment of AUD with a clinical perspective. Pharmacotherapies discussed include: disulfiram, acamprosate, naltrexone, nalmefene, topiramate, gabapentin, varenicline, baclofen, sodium oxybate, aripiprazole, ondansetron, mifepristone, ibudilast, suvorexant, prazosin, doxazosin, *N*-acetylcysteine, GET73, ASP8062, ABT-436, PF-5190457, and cannabidiol. Overall, many repurposed and novel agents discussed in this review demonstrate clinical effectiveness and promise for the future of AUD treatment. Importantly, these medications also offer potential improvements towards the advancement of precision medicine and personalized treatment for the heterogeneous AUD population. However, there remains a great need to improve access to treatment, increase the menu of approved pharmacological treatments, and de-stigmatize and increase treatment-seeking for AUD.

Key Points

Alcohol use disorder is severely under-treated, and the development of new and more effective pharmacotherapies is necessary.

The repurposed and novel agents discussed in this qualitative literature review offer promise for the future of AUD treatment, including advancements toward precision medicine for the heterogeneous AUD population.

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1 Introduction

Alcohol use disorder (AUD) is a highly prevalent, chronic, relapsing condition characterized by an impaired ability to stop or control alcohol use despite clinically significant impairment, distress, or other adverse consequences [1, 2]. It is the most common substance use disorder: in 2016, 100.4 million people globally were estimated to have an AUD [3]. This disorder represents a significant public health concern. The WHO estimates that alcohol consumption is responsible for 5.9% of all deaths (7.6% in men, 4.0% in women) and 5.1% of global disease burden [4]. Alcohol use and misuse is thought to contribute to over 200 related diseases and health conditions globally, including cardiovascular disease, cancer, liver cirrhosis, and injuries [4]. AUD is also often comorbid with other substance use disorders, major depressive disorder, bipolar disorder, and other psychiatric disorders [2].

In the USA alone, AUD is estimated to contribute to about 88,000 deaths each year [5]. An estimated 44.6 million adults per year in the USA suffer from AUD, and 93.4 million (approximately 33%) adults in the USA will meet or have met AUD criteria at some point in their life [2].

Furthermore, the economic burden of AUD is estimated to be approximately $250 billion across the USA [6].

Although AUD is an important public health concern, the disorder remains severely under treated with only 7% of adults with AUD in the USA [7] and less than 10% in Europe [8] receiving pharmacotherapy and/or psychotherapy treatment. Furthermore, the lag between the age at which AUD onsets and the age of first AUD treatment has been estimated to be eight years on average [7]. Pharmacotherapies have seen limited use in the treatment of AUD, partially due to lack of addiction treatment training for medical professionals, lack of awareness regarding medication options (e.g., limited marketing), reluctance to prescribe and take medications, perceived low efficacy of medication, and stigma surrounding treatment. Indeed, only three pharmacotherapies are approved by the US Food and Drug Administration (FDA) for use in AUD treatment. These medications are disulfiram (Antabuse), acamprosate, and naltrexone (formulated for oral administration or extended-release injection) [9–11]. The European Medicines Agency (EMA) similarly recognizes only these same three medications, as well as nalmefene, as established pharmacotherapies for AUD [12]. These medications are only modestly effective [13] and are under-utilized in treatment. A study conducted in 2019 found that only 1.6% of adults in the USA with past-year AUD received evidence-based AUD pharmacotherapies [14].

Treatment outcomes for AUD differ widely across patients and medications. While abstinence may be desirable, it is infrequently obtained, such that only 16% of individuals in treatment for AUD achieve abstinence [15]. Furthermore, evidence does not support abstinence as the only approach in the treatment of AUD [16]. Not all individuals with AUD consider abstinence to be a goal of their recovery; only 2–6% of goals set in patient-driven treatment center on attaining alcohol abstinence [17]. Non-abstinent recovery, including reductions in drinking and heavy drinking in particular (e.g., controlled drinking / harm reduction), has been recognized to have health and societal value and has gained traction as a treatment target [18–20]. Indeed, non-abstinent AUD recovery has been shown to be sustainable for up to 10 years following treatment [21]. Despite growing recognition of the benefits of harm reduction, however, the most commonly prescribed pharmacotherapy to treat AUD remains disulfiram, a medication advised strictly for abstinence [22]. Furthermore, the heterogeneity of AUD suggests that it will be unlikely that one single medication will be effective for all individuals with an AUD. Therefore, there is a pressing need for the development of novel, diverse, and effective pharmacological treatment options for AUD with the hopes of increasing utilization and improving care. The focus of the current review is to summarize pharmacotherapies for AUD with a clinical perspective. Specifically, this review provides a brief overview of currently approved medications and identifies new and repurposed agents "on the horizon" for which evidence indicates a potentially effective application toward AUD treatment.

2 Pharmacological Treatments for AUD

The following sections examine pharmacotherapies approved or in-development for AUD. Medications were selected for this qualitative review by considering gaps in existing review articles and the expertise of all authors; information was gathered via qualitative PubMed literature searches. This review is organized into sections based on drug approval status, namely (a) approved medications, (b) repurposed (i.e., off-label) medications, and (c) novel agents. Within each medication section, we examine the basic mechanism of action, evaluate preclinical research testing the efficacy of the medication in mitigating alcohol-related behaviors in animal models, and review clinical findings from human laboratory studies and randomized controlled trials (RCTs) where available. We also examine the tolerability and potential personalized applications of each drug by identifying populations in which the drug may be particularly effective, and indicate treatment targets (drinking reduction, achievement, or maintenance of abstinence). This information is summarized in Table 1. We conclude by discussing future directions for the development of pharmacological treatments and precision medicine for AUD.

2.1 Approved Agents

This section briefly describes medications currently approved by agencies in many countries including the US FDA and EMA for the treatment of AUD: disulfiram, acamprosate, and naltrexone (oral and extended-release), as well as nalmefene, which is EMA-approved. This section also reviews baclofen and sodium oxybate, which are medications approved for AUD treatment by agencies in European countries but not by the FDA or EMA. As many of these pharmacotherapies have been extensively discussed in the literature, our review of these medications primarily focuses on clinical trials and recent meta-analyses.

2.1.1 Disulfiram

Disulfiram, the first medication FDA-approved for AUD treatment (in 1951), is an aldehyde dehydrogenase inhibitor that acts by blocking the metabolism of alcohol, increasing acetaldehyde concentration. Acetaldehyde, a toxic metabolite of ethanol, produces an alcohol-induced aversive response, characterized by nausea, vomiting, sweating, flushing, and heart palpitations [23]. Unsurprisingly, these unpleasant effects give disulfiram a relatively poor adherence

Table 1 Pharmacotherapies approved and under development for the treatment of AUD

Agent	Mechanism of action	Approval status	Preclinical results	Clinical results	Target outcome
Disulfiram	Aldehyde dehydrogenase inhibitor; dopamine beta-hydroxylase inhibitor	FDA- and EMA-approved for AUD	Mixed results: prevents heavy but not moderate drinking [297]; chronic alcohol induces disulfiram tolerance [298]	Mixed results; drinking outcomes improved with supervised administration [29–33]	Achieve and maintain abstinence
Acamprosate	Modulates glutamatergic activity	FDA- and EMA-approved for AUD	Reduced ethanol intake, withdrawal symptoms, place preference [299–302]	Mixed results; Reduced risk of relapse, increased cumulative abstinence duration [36, 44, 49]. Negative studies show no benefit over placebo [37–42]	Achieve and maintain abstinence
Naltrexone	Opioid receptor antagonist	FDA- and EMA-approved for AUD	Reduced binge drinking, ethanol preference, motor impairment and sedation [303–305]	Reduced risk of relapse, binge drinking, and craving [52–59]; modest effect sizes [62–64]	Achieve and maintain abstinence and reduce drinking
Nalmefene	Opioid receptor antagonist and partial agonist	EMA-approved for AUD; FDA-approved for opioid overdose	Reduced alcohol seeking, relapse and binge-like drinking, neuroinflammation [306–308]	Reduced binge drinking and total alcohol consumption [71–73, 75]	Reduce drinking
Baclofen	$GABA_B$ agonist	Approved for AUD in France	Reduced ethanol self-administration and motivational properties [309–312]	Mixed results; increased rates of abstinence, time to first relapse, possibly reduced heavy-drinking days [84–86, 91, 92]	Achieve and maintain abstinence
Sodium oxybate	Modulates GABA activity	Approved for AUD in Italy and Austria	Reduced ethanol self-administration, withdrawal symptoms, and relapse-like drinking [247, 313]	Effective treatment of alcohol withdrawal syndrome, increased abstinence [99, 100]	Reduce withdrawal symptoms and achieve abstinence
Topiramate	Inhibits glutamatergic activity and increases GABA activity	Repurposed	Reduced ethanol intake in rodent models [113–115]	Reduced drinks per day and percent heavy-drinking days and increased percent days abstinent [112, 116–119]	Achieve abstinence and reduce drinking
Gabapentin	Modulates GABA activity	Repurposed	Mixed results: reduced or increased ethanol intake [123–125]	Reduced percent heavy-drinking days, alcohol consumption, and abstinence rates and increased time to relapse, with outcomes improved among those with alcohol withdrawal symptoms [126–135]	Achieve abstinence and reduce drinking
Varenicline	Nicotinic acetylcholine receptor agonist	Repurposed	Reduced ethanol seeking, intake, and binge-like consumption [138–140]	Reduced percent heavy-drinking days and drinks per day with outcomes improved for those who smoke cigarettes [142–144, 146–149]	Reduce drinking
Aripiprazole	Dopamine receptor partial agonist and 5-HT2A receptor antagonist	Repurposed	Reduce ethanol-induced place preference and ethanol consumption [151–153]	Mixed results with outcomes improved for more impulsive individuals; reduced heavy-drinking days and increased days abstinent at rates comparable to naltrexone [154–160]	Reduce drinking
Ondansetron	5-HT3 receptor antagonist	Repurposed	Blocked sensitization to locomotor stimulant effects, reduced voluntary ethanol intake [167–169]	Reduced drinks per day and increased days abstinent in patients with early-onset AUD [170–174]	Achieve abstinence and reduce drinking

Table 1 (continued)

Agent	Mechanism of action	Approval status	Preclinical results	Clinical results	Target outcome
Mifepristone	Glucocorticoid receptor antagonist	Repurposed	Reduced ethanol-seeking in rodents [177, 178] Mixed results in primates; reduced chronic voluntary alcohol use but did not prevent relapse [179, 180]	Reduced alcohol craving and consumption [178, 181, 182]	Reduce drinking
Ibudilast	Selective PDE inhibitor and MIF inhibitor	Repurposed	Reduced ethanol intake [188–191]	Reduced craving, odds of heavy drinking, and neural cue-reactivity [192, 193]	Reduce drinking
Prazosin and Doxazosin	Adrenergic alpha-1 antagonists	Repurposed	Reduced relapse, ethanol intake, and stress-induced ethanol seeking [201–205]	Mixed results; reduced craving and alcohol consumption. Outcomes improved among those with alcohol withdrawal symptoms [206–211]	Reduce drinking
N-Acetyl-cysteine	Modulates synaptic glutamatergic activity	Repurposed	Reduced ethanol intake and relapse [215–220]	Increased abstinence rates and reduced drinks per week among those with cannabis use disorder [222, 223]	Reduce drinking
Suvorexant	Dual orexin antagonist	Repurposed	Reduced ethanol consumption and relapse [229–238]	–	Unknown
ABT-436	Highly selective vasopressin type 1B receptor antagonist	Novel agent	Attenuated ethanol reinstatement and reduced ethanol intake [241, 242]	Increased days abstinent but did not reduce heavy drinking or craving [244]	Achieve and maintain abstinence
GET73	Gamma-hydroxybutyrate analogue; negative allosteric modulator at mGluR5	Novel agent	Reduced ethanol intake and suppressed relapse [246]	–	Unknown
ASP8062	Positive allosteric modulator of $GABA_B$ receptor	Novel agent	Reduced ethanol self-administration [259]	–	Unknown
PF-5190457	Ghrelin receptor inverse agonist	Novel agent	Reduced ethanol intake and preference [266–270]	Reduced alcohol craving and cue-reactivity [272]	Unknown
Cannabidiol	Diverse pharmacological effects	Novel agent	Reduced ethanol administration and relapse-like behavior [279]	–	Unknown

5-HT3 serotonin receptor 3, *5-HT2A* serotonin receptor 2A, *AUD* alcohol use disorder, *EMA* European Medicines Agency, *FDA* United States Food and Drug Administration, *GABA* gamma-aminobutyric acid, *mGluR5* metabotropic glutamate receptor 5, *MIF* macrophage migration inhibitory factor, *PDE* phosphodiesterase

rate [24, 25]. Disulfiram may also act on dopamine systems, as its major metabolite inhibits the enzyme dopamine beta-hydroxylase (DBH), which aids in metabolizing dopamine into noradrenaline [22, 26, 27]. Serum DBH activity is associated with withdrawal symptoms, and disulfiram has been shown to reduce serum DBH levels [28].

A meta-analysis of 22 RCTs found that disulfiram saw increased success rates compared to placebo in open-label studies only—blinded trials yielded no statistical significance between disulfiram and placebo [29]. However, while these findings do not appear to support the use of disulfiram for treating AUD, this outcome may be due to placebo effects. Research showed that placebo-treated individuals showed decreases in cue-reactivity to alcohol stimuli in a sample of 38 participants [30], and experiencing an acetaldehyde reaction did not necessarily improve treatment response in a sample of 46 participants [31]. Instead, a patient simply being aware of a potential adverse reaction appears to be enough to influence drinking behavior [32].

Disulfiram ingestion under supervision (to ensure adherence) saw significantly better success rates compared to non-supervised treatment, suggesting that supervised administration of disulfiram may still have a place in treating individuals struggling to attain sobriety [33], and unsupervised disulfiram may also be helpful for individuals highly motivated for abstinence. However, adherence management issues limit the utility of disulfiram in the treatment of AUD, and the disulfiram-ethanol interaction can sometimes present as a medical emergency. Therefore, disulfiram is only recommended in the maintenance of abstinence; using this medication to reduce drinking is not advised [34].

2.1.2 Acamprosate

While the specific mechanisms through which acamprosate works to treat AUD remain under investigation, it is thought to act on the glutamatergic system as an *N*-methyl-D-aspartic acid (NMDA) receptor partial co-agonist [35]. This may reduce neuronal hyperexcitability, a phenomenon that occurs in acute withdrawal and protracted abstinence from alcohol.

A meta-analysis of 27 RCTs with a total of 7519 participants found that acamprosate treatment reduced risk of abstinent patients returning to any drinking, but did not reduce rates of binge drinking [36]. A number of trials have also found that acamprosate did not show a significant benefit over placebo [37–41]. In particular, a large scale trial (COMBINE), which compared acamprosate, naltrexone, and behavioral therapies, both individually and combined with each other, against placebo ($N = 1383$), found that acamprosate had no significant effect on drinking in comparison to placebo, either alone or in combination with naltrexone and/or behavioral intervention [42]. Placebo effects in this trial may explain some of these negative outcomes, as might differences in trial design and patient characteristics: COMBINE required 4 days of pre-trial abstinence while European trials with positive outcomes were typically conducted in inpatient populations requiring complete detoxification [43]. Overall, however, a Cochrane meta-analysis of 24 RCTs with 6915 participants found that acamprosate significantly reduced the risk of any drinking and increased cumulative duration of abstinence [44].

Acamprosate is generally well tolerated [34] and may also have neuroprotective effects [45, 46]. As chronic alcohol abuse is associated with neuronal changes related to NMDA receptors, this neuroprotection may be particularly important in AUD treatment [47, 48]. Acamprosate is recommended for the achievement and maintenance of complete abstinence, rather than for the reduction of drinking or prevention of relapse in the event of drinking [49]. It is FDA-approved for abstinence maintenance in AUD patients who are abstinent when beginning treatment.

2.1.3 Naltrexone (Oral and Extended-Release)

Naltrexone, the best-studied of these three commonly approved medications, was originally approved to treat opioid use disorder. Naltrexone is an antagonist of the mu opioid receptor (with additional affinity for kappa and delta opioid receptors). By attenuating alcohol-induced opioidergic activity in the mesolimbic dopamine system, opioid antagonists like naltrexone, modulate the rewarding effects of alcohol (mediated by dopamine), thereby reducing alcohol consumption [50, 51].

In 1994, the FDA approved oral naltrexone to treat alcohol dependence after two independent 12-week trials, which included 97 and 70 participants, respectively, found that naltrexone significantly decreased drinking days and relapse rates [52, 53]. Additional recent trials demonstrate that naltrexone reduces the rewarding effects of alcohol [54, 55], alcohol craving [40, 56], drinks per drinking day [57], and relapse rates [58, 59], strengthening the initial findings.

Extended-release injectable naltrexone (i.e., Vivitrol), administered once monthly by a medical professional, may be beneficial for individuals who are more sensitive to naltrexone's adverse side effects or have difficulty adhering to oral medication [60]. A six-month multisite trial of 380 mg injectable naltrexone in 624 patients with alcohol dependence found significant reductions in heavy-drinking days versus placebo [61]. However, evidence for naltrexone remains mixed. Another RCT reported no significant differences between naltrexone and placebo ($N = 183$), and that the clinical utility of naltrexone was limited by its adverse effects [62]. Additionally, clinical trials of naltrexone often yield modest effect sizes [63]. A meta-analysis of 53 naltrexone RCTs with a total of 9140 participants found naltrexone

to significantly reduce both the risk of return to any drinking and return to binge drinking [36]; however, both of these associations were modest in magnitude [64].

Oral and injectable naltrexone show similar decreases in likelihood of binge drinking [65] and both are generally well tolerated, with fairly mild side effects [66]. Importantly, however, naltrexone does block the therapeutic effects of opioid analgesics and can precipitate opioid withdrawal in patients who have developed physical dependence to opioids [34]; therefore, individuals who are prescribed naltrexone for AUD must be monitored for opioid use and withdrawal. Of note, naltrexone is contraindicated for patients with acute hepatitis or liver failure, and should be "carefully considered" in patients with acute liver disease [67], potentially limiting its use in the alcohol-associated liver disease (AALD) population. In summary, naltrexone appears to have a moderate effect on the reduction of alcohol use.

2.1.4 Nalmefene

Nalmefene works in a similar manner to naltrexone as an antagonist at the mu and delta opioid receptor, but is also a kappa opioid receptor partial agonist [68]. Via its kappa agonist activity, particularly centered in dopaminergic nucleus accumbens circuitry, nalmefene may reduce motivation for self-administration and withdrawal-induced alcohol consumption [69, 70].

Nalmefene was approved by the EMA in 2013 for the reduction of alcohol consumption among patients with AUD. Approval followed findings from three multicenter 6-month clinical trials enrolling 604, 667, and 718 individuals, respectively, in which participants took the medication or placebo on an as-needed basis [71–73]. In these trials, nalmefene decreased total alcohol consumption and heavy-drinking days. However, the drug's approval based on these studies has received criticism due to limited evidence of efficacy, especially as these trials were conducted only against placebo rather than an active medication comparison (e.g., naltrexone) [34, 74]. A more recent meta-analysis of the efficacy of nalmefene, which included five RCTs (N = 2567), found that participants treated with nalmefene had 1.65 fewer heavy-drinking days per month than participants treated with placebo after 6 months [75].

Studies indicate that nalmefene is associated with more adverse events and study dropouts compared to placebo, and the most frequently reported of these are dizziness, nausea, vomiting, insomnia, and headache [36, 76]. Overall, while nalmefene may reduce heavy-drinking rates, its effects on other outcomes [77] remain small-to-moderate, and study withdrawals related to adverse events are common in nalmefene trials. However, similar to naltrexone, this medication may appeal to patients with goals of reducing alcohol consumption and those reluctant to engage in abstinence-based treatment.

2.1.5 Baclofen

Baclofen acts on the γ-amino butyric acid (GABA) system as a $GABA_B$ agonist. It was approved for treatment of AUD in France in 2018 [78] and has been used off-label for AUD for over a decade in other countries, especially other European countries and Australia [79, 80].

Clinical trials of baclofen have produced mixed results [65–67]. A recent meta-analysis of 12 RCTs (N = 703) showed that baclofen in comparison to placebo was associated with higher abstinence rates [81–83]; however, it did not increase abstinent days or decrease craving, heavy drinking, depression, or anxiety [84]. Another meta-analysis of 13 RCTs (N = 1492) indicated that baclofen (again vs placebo) was associated with longer time to relapse and a larger percentage of abstinent patients [85]. Furthermore, greater alcohol use at baseline was correlated with a greater treatment effect [85]. In contrast, however, another recent meta-analysis of 12 RCTs with 1128 total participants found no significant differences between baclofen and placebo in primary (i.e., percent abstinent days, percent heavy-drinking days, return to any drinking, and study dropout) or secondary outcomes of interest (i.e., anxiety and craving); however, baclofen did increase depression and adverse effects including sedation and vertigo [86].

Baclofen's significant adverse side effects include drowsiness, sedation, headache, vertigo, confusion, perspiration, muscle stiffness and/or abnormal movements, slurred speech, and numbness [86–88]. Tolerance to baclofen may also develop with chronic administration [89, 90]. Additionally, dose and sex may moderate baclofen tolerability and response; escalation of dosage in response to developing tolerance can increase sedative side effects, which affect women significantly more than men at the same dose [91]. Importantly, cessation or reduction in dose can precipitate potentially life-threatening withdrawal syndrome [90].

The variability in baclofen's effectiveness seen across studies may be partially explained by high baclofen pharmacokinetic variability seen among individuals with AUD. This heterogeneity is an important factor to take into account when considering baclofen as an AUD treatment [92]. Of note, there is also some evidence that baclofen might be particularly useful in treatment of AUD among individuals with liver disease [93, 94].

In summary, baclofen seems to effectively promote abstinence; however, it shows mixed results regarding its clinical effects on non-abstinence outcomes (e.g., reduction in heavy drinking), significant adverse side effects, and inter-individual variability in response. As such, baclofen as a treatment

of AUD—as well as its optimal dosage—continues to be debated [95].

2.1.6 Sodium Oxybate

Sodium oxybate (SMO), the sodium salt of gamma-hydroxybutyrate (GHB), has been utilized as a medication for a number of disorders. SMO is approved in Italy and Austria for the treatment of AUD [96]. SMO acts on the GABA system both directly as a $GABA_B$ partial agonist and indirectly through GHB-derived GABA [97, 98].

A Cochrane meta-analysis of 13 RCTs with a total of 649 participants found that SMO (50 mg) was effective compared to placebo in the treatment of alcohol withdrawal syndrome (AWS) and in preventing relapses in previously detoxified participants, and that SMO was more effective than naltrexone and disulfiram in maintaining abstinence [99]. Another recent meta-analysis found that SMO, compared to placebo, increased abstinence rates by up to 34% in a sample of 711 participants with very high drinking risk levels [100]. However, use of GHB as a recreational drug raises concern regarding the abuse potential of SMO. Indeed, in another clinical study with a sample of 48 participants, craving for SMO was observed in 10% of participants with psychiatric comorbidities [101], indicating that patients may be at risk of developing craving for and abusing SMO.

SMO may be particularly effective in combination with other pharmacotherapies. It was shown to reduce relapses when administered with naltrexone and escitalopram [102]. A study of 52 subjects with chronic, treatment-resistant alcohol dependence found that participants stayed in treatment significantly longer when SMO was co-administered with disulfiram than with SMO alone [103]. Additionally, in a case study of seven partial- and non-responders to SMO treatment, co-administration with nalmefene was effective in promoting abstinence, reducing heavy-drinking episodes, and importantly, suppressing craving for SMO [104].

SMO craving and abuse potential may limit its use; however, at therapeutic doses, SMO abuse seems to be a relatively infrequent phenomenon among patients without psychiatric comorbidities or poly-drug use [96, 100, 105]. Safety data show that serious adverse events with SMO treatment are rare, with the most common adverse effects being transitory dizziness and vertigo [96]. Overall, the effectiveness of SMO lies largely in reducing withdrawal symptoms and increasing abstinence rates. Its therapeutic use remains controversial due to its potential for craving and abuse, and further study on co-administration with other pharmacotherapies appears promising.

2.2 Repurposed Agents

The following sections address medications that have been approved by the FDA for applications other than AUD but are in development to be repurposed (i.e., used off-label) to treat AUD.

2.2.1 Topiramate

Despite that the anti-convulsant medication topiramate has not been approved by the FDA or EMA for AUD treatment, the US Department of Veterans Affairs recommends topiramate as a treatment for AUD, and it has been suggested by the American Psychiatric Association (APA) for the pharmacological treatment of patients with AUD [106, 107]. Currently, the specific mechanisms of action of topiramate remain under investigation. However, the drug is thought to inhibit glutamate α-amino 3-hydroxy-5-methyl-4-isoxazole-proprionic acid (AMPA) and kainate receptors [108–110] and L-type calcium channels [111], as well as enhance the inhibitory activity of GABA [109]. These effects, taken together, work to attenuate dopaminergic activity mesolimbic reward circuits, thereby reducing both alcohol craving and withdrawal symptoms [112].

Preclinically, topiramate was seen to decrease ethanol consumption in rodent models [113–115]. Clinical studies have found that topiramate reduced craving and alcohol drinking in a sample of 150 participants over 12 weeks [112], and decreased drinking days, heavy-drinking days, and number of drinks per day in a sample of 85 participants in a 14-week trial [116]. A large, multisite 14-week RCT that enrolled 371 participants with alcohol dependence found reductions in heavy-drinking days and improvements in various self-reported drinking-related outcomes [117]. A meta-analysis including seven RCTs of topiramate for AUD with a total of 1125 participants found that topiramate significantly increased number of days abstinence and decreased heavy-drinking days compared to placebo [118]. Of interest, this meta-analysis also directly compared effect sizes for topiramate and naltrexone, finding that topiramate was significantly more effective than naltrexone in reducing binge drinking, but not in improving abstinence [118]. Another recent month-long study of 94 patients that directly compared topiramate and baclofen demonstrated that baclofen was overall more effective (i.e., 61% of participants receiving baclofen achieved abstinence vs 38% with topiramate) and better tolerated (i.e., 33% of participants receiving topiramate dropped out of the study vs 24% with baclofen) than topiramate [119].

The potential of reduced tolerability and significant side effects such as pruritis, paresthesia, anorexia, dysgeusia, dizziness, nervousness, and cognitive impairment, including difficulty with concentration and attention, are concerns for

the use of topiramate in the treatment of AUD [50]. These cognitive impairments were found to be dose-associated and include impairments in working memory and verbal fluency, as well as mental slowing [116]. Topiramate's side effects, especially those affecting memory and cognition, present reasons for concern and warrant long-term trials to further investigate these effects. Slow dose titration and ongoing patient monitoring is also recommended.

It is worth noting a potential strength of topiramate: the possibility of starting treatment while patients are still actively drinking, allowing topiramate to serve as a harm-reduction or abstinence-initiation treatment, rather than only being used to prevent relapse in already detoxified patients [120]. Topiramate has already been demonstrably effective in clinical applications across a number of drinking outcomes [121], but longer-term trials of topiramate are recommended to optimize dose and duration, as well as further exploring side effects.

2.2.2 Gabapentin

Another anti-convulsant medication, gabapentin, is also suggested by the APA for use in AUD treatment with the goal of reducing alcohol consumption or achieving abstinence [107]. It is thought to modulate GABA activity by indirectly interacting with voltage-gated calcium channels [122]. Preclinical studies of gabapentin's effects on ethanol consumption have shown mixed results, with some studies finding that gabapentin reduced ethanol intake in alcohol-dependent rodents [123] and others finding that it increased self-administration and binge-like drinking [124, 125].

Gabapentin has shown promising results in human laboratory studies and clinical trials. Gabapentin reduced percent heavy-drinking days and drinks per day, as well as increased percentage abstinent days in a 28-day trial with 60 participants [126]. In another 10-day study with 21 participants, gabapentin significantly delayed return to heavy drinking [127]. In a proof-of-concept one-week human laboratory trial ($N = 33$), participants treated with gabapentin showed significant decreases in alcohol craving in comparison to placebo [128], and a follow-up 12-week RCT with 150 participants found that gabapentin significantly increased abstinence rates and percentage of no heavy-drinking days [129]. Gabapentin may also be particularly effective in combination with other medications. For instance, a combination of gabapentin and flumazenil over 39 days in 60 participants increased percentage of abstinent days and delayed time to first heavy-drinking day compared to placebo. This trial also showed an interaction effect with pre-study alcohol withdrawal, such that those with more severe withdrawal symptoms at baseline benefitted more from the treatment during the trial [130]. In combination with naltrexone, gabapentin was also shown to be more effective (i.e., decreased heavy-drinking days, fewer drinks per drinking day, and delayed time to heavy drinking) compared with naltrexone alone in a 6-week trial with 150 participants [131].

A Cochrane review of 25 studies ($N = 2641$) found anticonvulsants, including gabapentin, to significantly reduce both heavy-drinking days and drinks per drinking day in comparison to placebo. Anticonvulsants were also associated with longer time-to-relapse and fewer heavy-drinking days compared to naltrexone [132]. A recent meta-analysis of 7 RCTs with a total of 751 participants found that gabapentin compared to placebo only significantly decreased percent heavy-drinking days, although trend-level effect estimates were shown for other alcohol-related outcomes (i.e., relapse, drinks per day, complete abstinence, percent days abstinent, and concentration of gamma-glutamyl transferase (GGT)) [133]. In a 16-week RCT with 96 participants, gabapentin improved the percentage of individuals with no heavy-drinking days and increased total abstinence rates over placebo, especially among participants with more severe pre-study withdrawal [134]. However, another recent 6-month multisite RCT of extended-release gabapentin conducted in 346 participants with at least moderate AUD found no effects over placebo for any clinical outcomes including abstinence rate, percent heavy-drinking days, drinks per drinking day, or alcohol craving [135]. While these findings may be related to potential pharmacokinetic issues relating to the specific formulation of extended-release gabapentin used in the trial, it is also possible that gabapentin may simply be more effective in patients with more clinically relevant and severe symptoms of alcohol withdrawal [130, 134].

The most common adverse events associated with gabapentin treatment are somnolence, dizziness, peripheral edema, and ataxia or gait disorder [136]. Notably, gabapentin does carry the potential for misuse and abuse, particularly in individuals with opioid use disorders [137]; therefore, recommendation of gabapentin to individuals with comorbid substance use disorder should be carefully considered. In summary, gabapentin shows some clinical efficacy, especially in populations with more severe withdrawal symptomology, but more extensive investigation is recommended.

2.2.3 Varenicline

Varenicline is a nicotinic acetylcholine receptor agonist (partial at α4β2; full at α7) that is used for the treatment of nicotine dependence. In rodent models, varenicline was shown to reduce ethanol seeking, intake, and binge-like consumption [138–140]. Additionally, the combination of varenicline and naltrexone decreased alcohol drinking more effectively than either drug on its own [141].

Clinically, varenicline was found to significantly reduce weekly percent heavy-drinking days, drinks per day, drinks per drinking day, and alcohol craving compared to placebo

in a 13-week multisite RCT with 200 participants [142]. However, a 12-week RCT ($N = 160$) found no effect of varenicline over placebo on heavy-drinking days [143], and a recent 6-week human laboratory study in 47 participants found that varenicline did not significantly attenuate cue-induced alcohol craving relative to placebo [144].

Varenicline appears to be especially relevant to heavy-drinking smokers. Approximately 20%–25% of current smokers are estimated to also be heavy drinkers [145]. A human laboratory study with 20 heavy-drinking smokers on varenicline for 7 days found that varenicline significantly reduced the number of drinks consumed and increased the likelihood of complete abstinence in the human laboratory paradigm [146]. Moderator analyses of data collected in the above multisite trial [142] indicated that varenicline was more efficacious in reducing drinking among smokers who also reduced their cigarette smoking [147] and among individuals with lower severity of AUD, such that that varenicline significantly reduced percent heavy-drinking days and drinks per drinking day in low-severity individuals, while the most severe group showed no differences between varenicline and placebo on drinking outcomes [148].

Findings also indicate that varenicline may be more effective as an AUD treatment in men, as a 16-week RCT with 131 participants found that varenicline combined with medication management decreased percent heavy-drinking days only in men, but improved smoking abstinence in both men and women [149]. Varenicline is well tolerated, suggesting that it may serve as a promising option for AUD treatment, especially in the case of individuals co-using alcohol and nicotine.

2.2.4 Aripiprazole

Aripiprazole is an antipsychotic drug that acts as a partial agonist at the dopamine D2 and 5-HT1A receptors and as an antagonist at the 5-HT2A receptor [150]. Preclinically, aripiprazole has been shown to reduce ethanol-induced place preference and decrease drinking behaviors in mice [151], as well as reducing alcohol consumption in alcohol-preferring rats [152, 153].

A human laboratory study in 18 healthy participants indicated that aripiprazole affected outcomes related to alcohol consumption (i.e., subjective response to alcohol), including reducing the euphoric effects of alcohol and increasing sedative effects [154]. In a sample of 30 participants with AUD, aripiprazole compared to placebo, was found to attenuate cue-induced neural activation in the ventral striatum, a region associated with reward [155]. Another recent clinical laboratory study in which 99 participants with AUD took aripiprazole over eight days found that aripiprazole reduced the number of drinks consumed in a bar lab setting, especially among individuals with low self-control, and prolonged the latency to drink in individuals with high impulsivity [156].

Results from clinical trials of aripiprazole are mixed. A 16-week RCT directly comparing aripiprazole against naltrexone ($N = 75$) found that the two medications were overall comparable in reducing heavy-drinking days and increasing days of abstinence, although patients treated with naltrexone had reduced craving compared to aripiprazole [157]. A 35-day open-label trial assessing the combination of aripiprazole and topiramate in 13 heavy-drinking participants found significant reductions in alcohol use. Additionally, this trial provided no evidence that the side effects of the two medications are additive, indicating that the combination is generally safe and well tolerated [158]. However, another recent five-week study assessing topiramate, aripiprazole, and their combination with 90 participants found that effects on drinking reduction were due to topiramate, while no significant findings were seen for aripiprazole for any outcomes [159]. Another multicenter RCT enrolling 295 participants over 12 weeks found no significant difference between the aripiprazole and placebo groups in percentage of participants completely abstinent from alcohol throughout the study or time to first drinking day; however, the average number of drinks per drinking day was significantly lower for aripiprazole [160]. The aripiprazole group yielded significantly higher discontinuation rates and earlier discontinuation, largely due to adverse events associated with side effects, especially when dosage exceeded 15 mg/day. The most common side effects cited in cases of discontinuation were fatigue, insomnia, restlessness, anxiety, and deficits in attention. Of note, long-term use of antipsychotics like aripiprazole may be associated with more severe adverse effects such as tardive dyskinesia, with risk factors including older age and female sex [161, 162].

In summary, these findings suggest that aripiprazole may be more effective at lower doses and in more impulsive individuals, although larger confirmatory studies are needed to pursue these personalized medicine approaches.

2.2.5 Ondansetron

Ondansetron is a 5-HT3 antagonist that is used to treat nausea and vomiting. Although the specific mechanism of action remains under investigation, ondansetron may address serotonergic dysfunction common in early-onset AUD [163, 164], and may reduce alcohol craving via 5-HT3 projections to dopaminergic connections in the midbrain. Preclinically, 5-HT3 antagonism has been shown to block acquisition and maintenance of ethanol self-administration [165] and reduce ethanol-associated dopamine concentration in the nucleus accumbens [166]. Ondansetron was also found to block the development and expression of sensitization to the

locomotor stimulant effects of ethanol [167] and reduce voluntary ethanol intake, preference, and withdrawal seizures in rodent models [168, 169].

Clinically, ondansetron may be particularly effective in combination with naltrexone. In an 8-week RCT in 20 participants with early-onset AUD, ondansetron and naltrexone (in comparison with placebo) significantly reduced drinks per drinking day and trended towards an increase in percentage of days abstinent [170]. Another combination study in 90 participants after 7 days on ondansetron and naltrexone found that the combination decreased craving for alcohol and ventral striatal activation to alcohol cues [171].

Ondansetron may also be suitable for individuals with biological predisposition to early-onset AUD. In an 11-week RCT of 271 participants, ondansetron was shown to reduce self-reported drinking such that patients with early-onset AUD who received ondansetron reported fewer drinks per day and more days of abstinence compared to placebo [172]. Ondansetron, combined with cognitive behavioral therapy in an 8-week open-label trial ($N = 40$) comparing effects in early-onset versus late-onset AUD, found that drinks per drinking day and alcohol-related problems (i.e., Drinker Inventory of Consequences; DrInC) were significantly decreased among those with early-onset AUD compared to those with late-onset AUD [173]. Furthermore, in an 11-week study with 253 participants, ondansetron at 4 µg/kg reduced overall craving significantly in participants with early-onset AUD, while a lower dose (1 µg/kg) reduced craving in participants with late-onset AUD. These reductions in craving were also associated with reduced drinking (i.e., drinks per drinking day) and an increased percentage of abstinent days [174].

Ondansetron is well tolerated with relatively mild side effects including diarrhea, constipation, and headache [175]. Overall, these studies suggest a potential role for ondansetron as an AUD treatment, especially in participants with early-onset AUD and possibly in combination with naltrexone.

2.2.6 Mifepristone

Mifepristone (RU-486), a glucocorticoid receptor antagonist, works on the stress system by regulating the amygdala [176]. Preclinically, both systemic and central amygdala injections of mifepristone were shown to suppress yohimbine stress-induced reinstatement of alcohol seeking, indicating that the central amygdala plays an important role in mifepristone's effects on ethanol-seeking [177, 178]. Recent preclinical research in primates has shown mixed results, such that mifepristone was shown to decrease chronic voluntary alcohol consumption in rhesus macaques at doses of 30 and 56 mg/kg per day [179], but had no effect on alcohol-seeking or self-administration in baboons at slightly lower doses of 10–30 mg/kg per day [180]. Of note, in the former study, cessation of mifepristone treatment resulted in a rapid return to baseline intake levels, and mifepristone was not effective in preventing a relapse during early abstinence.

In a human laboratory study with 56 alcohol-dependent participants, mifepristone (taken for one week) was effective in reducing alcohol craving and consumption relative to placebo, improved liver-function markers, and was overall well tolerated [178]. A two-week Phase 4 RCT examining the effects of mifepristone on cognition in AUD was recently conducted, but recruitment challenges rendered the results inconclusive [181, 182]. Of note, in this trial, participants who received mifepristone had higher Beck Depression Inventory scores compared to placebo at 4 weeks post-randomization despite similar scores at baseline between the two groups, indicating a greater severity of depression symptoms caused by the medication. Additional clinical research on mifepristone as a treatment for AUD and its potential side effects is warranted.

2.2.7 Ibudilast

Ibudilast is an inhibitor of phosphodiesterases (PDE)-3, -4, -10, and -11 [183] and macrophage migration inhibitory factor (MIF) [184]. Ibudilast has been shown to dose-dependently suppress pro-inflammatory cytokines, such as interleukins IL-1β, IL-6, and tumor necrosis factor alpha (TNF-α), and to increase the anti-inflammatory cytokine IL-10 and neurotrophic factors [185]. As increases in inflammation are seen in AUD [186], the effects of ibudilast in treating AUD are thought to be driven by its anti-inflammatory and pro-neurotrophic qualities [187].

Preclinically, ibudilast was demonstrated to reduce alcohol intake in two rat models, and decreased drinking selectively in alcohol-dependent mice in comparison to non-dependent mice [188]. These preclinical findings align with prior rodent studies in which pharmacological inhibition of PDE also reduced alcohol intake [189–191].

In a 7-day human laboratory crossover trial ($N = 24$), ibudilast was well tolerated and decreased tonic craving in comparison to placebo. Additionally, ibudilast improved mood during exposure to alcohol and stress cues, and reduced the mood-altering and stimulant effects of alcohol among participants with more severe depressive symptoms [192]. Another recent 2-week RCT enrolling 52 participants found that ibudilast also significantly decreased the odds of heavy drinking during the trial by 45% compared to placebo and attenuated neural response to alcohol cues in the ventral striatum [193, 194].

Ibudilast appears to be well tolerated [195], with common adverse side effects including gastrointestinal symptoms (nausea, vomiting, abdominal pain, and diarrhea),

headaches, and depression [192, 196]. In the aforementioned 2-week RCT, no significant differences in side effects were seen between groups [193]. In summary, early findings from clinical studies of ibudilast for AUD treatment appear promising and warrant further clinical investigation.

2.2.8 Prazosin and Doxazosin

Prazosin and doxazosin are alpha-1 adrenergic receptor antagonists with similar chemical structures that can readily cross the blood-brain barrier and block noradrenergic excitation of the mesolimbic dopaminergic system [197, 198]. Both medications are used for the treatment of hypertension and benign prostatic hyperplasia. While these medications show good safety and tolerability, doxazosin appears to have a better clinical profile, such as improved absorption profile and a longer half-life, leading to less frequent dosing. Adrenergic receptors regulate sympathetic nervous system activity through activation of the neurotransmitter norepinephrine [199]. Stress physiology is disrupted with chronic alcohol use, particularly during early alcohol abstinence. In early abstinence, individuals with AUD experience more emotional dysregulation, stress, and alcohol cravings, all of which can increase the risk of relapse. Thus, alpha-1 blockers like prazosin and doxazosin may help to normalize these stress system changes seen in AUD [200].

Preclinical work found that prazosin reduced ethanol-related operant responding in acute withdrawal for dependent, but not non-dependent rodents [201]. In addition, prazosin treatment prevented yohimbine stress-induced reinstatement of ethanol seeking [202] and attenuated ethanol intake during relapse in alcohol-preferring rats [203]. Doxazosin decreased voluntary alcohol intake in alcohol-preferring rats in a dose-dependent manner, and this effect was likely not due to general motor impairment [204]. Further, doxazosin significantly reduced voluntary ethanol intake in a rodent model of AUD and stress exposure [205].

In humans, an early 6-week pilot study with 24 randomized participants with AUD revealed that prazosin treatment was associated with fewer drinking days per week and fewer drinks per week than placebo [206]. More recently, 92 participants with AUD completed a 12-week double-blind study with prazosin and medication management [207]. Results from intent-to-treat analyses showed that prazosin participants had greater reductions in heavy drinking and rates of drinking over time, although these effects were modest. A 10-week RCT comprising 41 individuals with AUD showed no significant effect of doxazosin over placebo on quantity of alcohol consumption (i.e., drinks per week, heavy-drinking days) [208]. However, further examination of clinical moderators revealed that doxazosin significantly reduced drinks per week and heavy-drinking days among individuals with higher family history of AUD and higher standing diastolic blood pressure [209]. Similarly, moderator analyses from a 12-week RCT of prazosin ($N = 100$) found that one's degree of alcohol withdrawal symptoms predicted clinical response, such that participants with high levels of withdrawal symptoms benefited the most from treatment (e.g., reduced craving and heavy-drinking days; improved mood symptoms) [210]. A small meta-analysis of 6 studies with a total of 319 participants tested the effectiveness of drugs acting on adrenergic receptors for AUD and found a significant treatment effect of prazosin and doxazosin on alcohol consumption but not abstinence [211]. In summary, prazosin and doxazosin show some early promise as a treatment for AUD and may be particularly beneficial as a harm-reduction approach and for individuals with significant alcohol withdrawal symptoms or family history of AUD as well as comorbid post-traumatic stress disorder (PTSD).

2.2.9 *N*-Acetylcysteine

Alcohol use has been shown to alter the glutamate system. Chronic and binge drinking inhibit glutamate levels and transmission through blockade of NMDA receptors, subsequently leading to elevated glutamate levels during alcohol withdrawal [212–214]. *N*-Acetylcysteine (NAC) is a cysteine prodrug that works to restore glutamatergic tone in reward circuitry by improving the expression and function of the cysteine-glutamate exchanger and normalizing glial glutamate transporters [215, 216].

Preclinically, NAC has been shown to reduce withdrawal effects [217], block the development of behavioral sensitization to alcohol [218], and attenuate biological adaptations induced by alcohol cessation (i.e., blocked the reduction of transcription factor ΔFosB in the nucleus accumbens; reduced corticosterone and leptin levels) [218–220]. Additionally, NAC reduced ethanol-seeking and self-administration in rodents [215, 216]. NAC and aspirin co-administration also reduced ethanol intake and relapse binge drinking in ethanol-preferring rats [221].

In a recent meta-analysis of seven RCTs with a total of 245 participants, NAC compared to placebo was shown to reduce craving symptoms across a number of substance use disorders [222]. A secondary analysis of a 12-week, multisite RCT of NAC to treat cannabis use disorder in 277 participants found that NAC increased odds of between-visit abstinence, and reduced alcohol consumption (i.e., drinks per week and drinking days per week) by 30% [223]. However, a recent 5-day human laboratory study ($N = 9$) found that NAC did not attenuate alcohol self-administration [212]. Additional clinical trials will also examine the effectiveness of NAC in adolescent and adult samples of AUD ([224], NCT03707951). These trials include samples with comorbid psychopathology (i.e., PTSD) and will use neuroimaging

methods to examine the neural circuitry underlying NAC's modulation of relevant metabolites and neural reactivity to alcohol cues.

Orally-administered NAC appears to be well tolerated, with the most common adverse effects being nausea and diarrhea [212, 222]. Of note, NAC is currently being tested in adolescent AUD, a unique prospect as no other AUD pharmacotherapies are yet approved for adolescents [225]. In summary, NAC represents a promising potential treatment for AUD and merits further exploration.

2.2.10 Suvorexant

Suvorexant is a dual orexin antagonist that is used for the treatment of insomnia. The orexin/hypocretin system is well known for its role in sleep-wake regulation but has more recently been implicated in AUD [226]. Orexins are neuropeptides that are densely localized in the lateral hypothalamus. Orexins A and B bind to the G-protein coupled orexin-1 and orexin-2 receptors. Orexin A has equal affinity for both receptors, whereas orexin B has selectivity for orexin-2 receptors. The dense orexin projections from the lateral hypothalamus to the ventral tegmental area provide neurobiological support that orexins may influence responses to rewarding stimuli, including alcohol [227, 228].

Animal models demonstrate that orexin-1 receptor antagonists reduce alcohol drinking in alcohol-dependent mice and alcohol-preferring rats [229–233]. Orexin-2 antagonists also reduce alcohol drinking and reinstatement/relapse in mice and rats [234–236]. Similarly, dual orexin antagonists reduce alcohol consumption in alcohol-preferring rats [237, 238]. Given the effectiveness of orexin antagonists in reducing alcohol drinking at the preclinical level of analysis, suvorexant has garnered interest as a drug that can be repurposed to treat AUD [239]. While no animal or human laboratory study has directly examined the efficacy of suvorexant on alcohol-related behaviors, two ongoing Phase 2 RCTs will assess suvorexant's potential as a treatment for AUD (NCT04229095) and comorbid AUD + insomnia (NCT03897062). The sedative effects of suvorexant are of notable concern, particularly if individuals engage in alcohol drinking during treatment [240]. Thus, the level of patient monitoring throughout the treatment phase and finding the optimal time of dosing to negate the additive sedative effects are important factors to consider to fully evaluate its therapeutic potential.

2.3 Novel Agents

The following sections discuss novel agents that have not yet been approved for any use. These medications are early in development and the majority do not yet have available clinical findings on their application toward the treatment of AUD.

2.3.1 ABT-436

ABT-436 is an orally active, highly selective vasopressin type 1B (V1B) receptor antagonist. V1B antagonists attenuate basal hypothalamic-pituitary-adrenal (HPA) axis activity and have shown favorable effects in rat models of alcohol dependence, including attenuating reinstatement of alcohol self-administration [241], and diminishing alcohol intake by alcohol-preferring and alcohol-dependent rats [241, 242].

ABT-436 has been shown to attenuate basal HPA axis activity in humans [243]. A 12-week RCT enrolling 150 participants found ABT-436 to be associated with an increased percentage of days of abstinence compared to placebo, as well as significantly reduced cigarette use [244]. However, no differences were found on heavy-drinking days or alcohol craving. A subgroup analysis also showed that ABT-436 appeared to have greater efficacy among participants with high baseline stress levels. This study was the first Phase 2 clinical trial that tested a V1B receptor antagonist for AUD.

The finding that ABT-436 reduced both alcohol drinking and smoking indicate a potential use for V1B antagonists to treat co-use of alcohol and nicotine. ABT-436 is generally well tolerated in humans, with the most common side effect being diarrhea. Furthermore, results indicate that patients with high levels of stress may specifically benefit from medications targeting the vasopressin receptor.

2.3.2 GET73

N-[(4-Trifluoromethyl) benzyl] 4-methoxybutyramide (GET73) is a GHB analogue that has shown promising in vitro and in vivo preclinical results as a potential agent for the treatment of AUD. The addition of GET73 to cultures of rat hippocampal neurons rescued negative ethanol-induced effects, reductions in cell viability, and increases in reactive oxygen species production, providing evidence for a neuroprotective role of GET73 as an AUD treatment [245]. In vivo, GET73 treatment at low, non-sedative doses (5–50 mg/kg) reduced alcohol intake and suppressed relapse in alcohol-preferring rats, as well as exerting anxiolytic effects [246]. These effects are similar to those seen with GHB administration [247]; however, GET73 was shown not to bind to either high- or low-affinity GHB binding sites in rat cortical membranes [246]. Recent studies indicate that GET73 may act as a negative allosteric modulator at the metabotropic glutamate subtype 5 receptor (mGluR5) [248]; however, the complete mechanism of action of GET73 remains unclear.

A translational study examining GET73-alcohol interactions found that neither 30 nor 100 mg/kg GET73

administered in rats (equivalent to doses employed in humans) potentiated alcohol-induced intoxication. Additionally, GET73 administered both in the presence and absence of alcohol was well tolerated in two samples of 14 and 11 participants, with no severe adverse events and no difference in adverse events [249]. A Phase I clinical trial in two samples of 48 and 32 participants found that both single doses (up to 600 mg) and repeated ascending doses (up to 450 mg twice /day) of GET-73 were safe and well tolerated [250]. Another inpatient human laboratory study conducted by the same group confirmed the safety and tolerability of GET73 such that no serious or severe adverse events occurred when GET73 was co-administered with alcohol. Co-administration also did not affect the pharmacokinetics of either GET73 or alcohol. However, GET73 also had no effect on alcohol cue-induced craving or self-administration, warranting additional research [251]. A clinical trial of the effects of GET73 on magnetic resonance spectroscopy (MRS) measures of glutamate and GABA levels in individuals with AUD was recently completed (NCT03418623); however, the results have not yet been posted, and another trial, which includes a free-drinking bar lab component, is ongoing (NCT04831684).

2.3.3 ASP8062

In comparison to the drawbacks presented by $GABA_B$ agonists like baclofen and SMO, positive allosteric modulators (PAMs) at this receptor present a potential alternative [252]. By binding to a different, non-competitive allosteric site on the $GABA_B$ receptor, PAMs allow endogenous GABA, binding at its original orthosteric site, to retain its potency and efficacy, reducing the risk of tolerance development and side effects [253, 254]. A number of PAMs have been studied as potential pharmacotherapies for AUD, and have demonstrated reductions in alcohol-associated behaviors and ethanol self-administration in preclinical models [252, 255–258]. When directly contrasted against baclofen, a $GABA_B$ PAM had a better profile, with dose-dependent reduction of relapse-like alcohol drinking and with no signs of sedation [257].

One such novel $GABA_B$ PAM, ASP8062, appears particularly promising as it has been shown to significantly increase the affinity and efficacy of endogenous GABA binding in human and rat $GABA_B$ receptors in vitro and with oral administration in an in vivo rodent model of fibromyalgia, demonstrating the ability of oral formulated ASP8062 to cross the blood-brain-barrier [259]. ASP8062 has recently progressed to clinical development. Two Phase I clinical trials with a combined total of 112 participants evaluated single ascending doses and multiple ascending doses of ASP8062, respectively [260]. These studies found that ASP8062 was well tolerated in humans, with no evidence of drug effects on safety, cognition, drug withdrawal, or suicidal ideation. One additional clinical trial, assessing the safety and efficacy of ASP8062 for alcohol use disorder (NCT05096117), is currently underway. Overall, ASP8062, and $GABA_B$ PAMs in general, appear to be well tolerated in humans and decrease alcohol self-administration in animals. These agents present a potential pathway to better utilize the GABAergic system and reduce the side effects seen with $GABA_B$ agonists.

2.3.4 PF-5190457

Ghrelin, a peptide produced by endocrine cells primarily in the stomach [261], is thought to regulate growth hormone secretion, food intake, and glucose homeostasis [262]. Ghrelin is also thought to play a role in AUD. Ghrelin signaling is required for stimulation of the reward system by alcohol, and higher ghrelin levels are associated with higher self-reported measures of alcohol craving [263]. In human laboratory studies, intravenous ghrelin administration has been shown to increase the urge to drink, increase alcohol self-administration, and modulate brain activity in regions involved in reward processing and stress regulation [264, 265].

Preclinical studies with ghrelin receptor (GHS-R1a) antagonists have shown reductions in alcohol conditioned place preference, alcohol intake and preference, and alcohol-elicited nucleus accumbens dopamine release in rodents [266–270].

PF-5190457 is a ghrelin receptor inverse agonist that inhibits GHS-R1a constitutive activity as well as blocking its activation by ghrelin [271]. In a preliminary clinical study in 12 heavy-drinking individuals, PF-5190457, compared to placebo, reduced alcohol craving and cue-reactivity to alcohol. Additionally, when administered in combination with alcohol, PF-5190457 was safe and well-tolerated with no drug-alcohol interactions [272]. This was the first clinical study of a GHS-R1a inverse agonist in a sample of heavy alcohol drinkers.

PF-5190457 may increase somnolence, heart rate, and lower blood glucose concentrations [273], although clinical results indicate that these side effects were not exacerbated by alcohol co-administration and in general PF-5190457 is well tolerated. In summary, preclinical and early clinical evidence support additional research toward investigating PF-5190457 as a pharmacological approach to treat AUD.

2.3.5 Cannabidiol

Cannabidiol (CBD), one of the main compounds found in *Cannabis sativa*, has shown promise as a novel therapeutic to treat AUD. CBD is nonintoxicating and has diverse pharmacological effects throughout the central nervous system, including functioning as a negative allosteric modulator of

CB_1 and CB_2 receptors [274, 275], and blocking anandamide update and inhibiting enzymatic hydrolysis [276]. CBD may also interact with non-endocannabinoid signaling systems, including the serotonergic system [277] and the opioidergic system [278], among others.

Preclinical studies have shown that CBD reduces alcohol administration, decreases motivation for alcohol, reduces relapse-like behavior, and improves withdrawal symptoms in animals exposed to chronic alcohol [279]. Evidence in healthy individuals demonstrates that CBD is well tolerated, does not interact with the subjective effects of alcohol, and has no abuse liability [280]. Two recent studies investigated signals for potential efficacy of CBD as a treatment for heroin use disorder [281] and cannabis use disorder [282]. Regarding heroin use disorder, acute CBD reduced cue-induced craving for heroin and reduced anxiety in a sample of 42 abstinent individuals, which was maintained one-week following the last CBD exposure. The cannabis use disorder study found that CBD was more efficacious at reducing cannabis use than placebo in a sample of 48 subjects. In both clinical samples, CBD was well tolerated and not associated with serious adverse events. CBD is currently being evaluated as a potential treatment for AUD, AUD with comorbid PTSD, and alcohol withdrawal in AUD in three clinical trials (NCT03252756, NCT03248167, NCT04205682). In brief, preclinical evidence and clinical evidence in other substance use disorders indicate the promise of CBD as a novel therapeutic for AUD.

3 Discussion

This qualitative literature review discusses the efficacy, mechanism of action, and tolerability of approved, repurposed, and novel pharmacotherapies for the treatment of AUD. This information is summarized in Table 1. As of 2018, the APA recommends acamprosate and naltrexone for the treatment of AUD and suggests gabapentin and topiramate for patients with the goal of reducing alcohol consumption or achieving abstinence, while disulfiram is suggested for achieving and maintaining abstinence only [107]. Similarly, while not included in the APA's recommendations, aripiprazole and mifepristone are associated with drinking reduction, while baclofen shows association with abstinence and mixed results with drinking reduction. Additional repurposed medications show clinical effectiveness for the treatment of AUD. Some of these appear to have particular promise in specific cases, such as varenicline's use for nicotine and alcohol co-users [147], baclofen for individuals with liver disease [93], and aripiprazole for more impulsive individuals [156]. Novel agents such as GET73 [245] and ASP8062 [260] have also reduced alcohol intake in preclinical studies. In summary, while currently approved medications are somewhat effective, there remains a crucial need to develop new and improved pharmacotherapies for AUD. Novel and repurposed agents show significant promise as treatments that may improve upon currently approved pharmacotherapies.

Medication development has been identified as a critical priority for AUD research [283]. While considerable progress has been made in this field, there are a number of areas which require our attention to realize the benefit of AUD pharmacotherapy. First, despite the prevalence of AUD, the rate of seeking treatment for AUD remains very low [284]. In order for anyone to benefit from the advances in medication development reviewed herein, the treatment gap must be closed. This will require engagement at multiple levels, from prevention to public education about AUD and the available treatments. Researchers and clinicians can help in these efforts by reducing stigma surrounding AUD and other substance use disorders by choosing appropriate language to describe these disorders and the people who are affected by them [285].

A related issue is the need to improve access to FDA-approved pharmacotherapies for AUD. A recent analysis of the 2019 National Survey on Drug Use and Health found that only 1.6% of people with a past-year AUD received an evidence-based medication to treat their AUD [14]. Medication use was associated with living in a large metropolitan area, use of the emergency department, and receiving mental health care, indicating that these services and residing in an urban environment appear to increase access to evidence-based medications. There is also a great need to improve the education of physicians and clinicians on the availability of evidence-based treatments for AUD. Ongoing efforts in this area are underway by the American Society of Addiction Medicine and the American Academy of Addiction Psychiatry, as well as by the National Institute on Alcohol Abuse and Alcoholism.

To further improve access to treatments and increase treatment-seeking, there is a need to increase the menu of approved pharmacological treatments towards AUD, especially those that have shown promise internationally. Currently, the FDA only accepts two primary outcomes for Phase 3 trials: abstinence and no heavy-drinking days. These outcomes do not always mirror the goals of patients with AUD for their recovery, which may be better reflected by a harm reduction endpoint. Recent work has found that harm reduction endpoints, including reductions in WHO-based drinking levels [286], are associated with improvements in physical health and quality of life [287] and can be used as efficacy outcomes in clinical trials [288]. The acceptance of these outcomes as clinical trial endpoints could have a substantial impact on the medication development field and ultimately result in a larger pharmacotherapy toolbox for clinicians.

Another area of development is the move towards personalized treatment, also referred to as precision medication. AUD is a highly heterogenous disorder, and it unlikely that any medication will work for all individuals with an AUD. As such, there have been efforts to use precision medicine approaches to tailor pharmacotherapies to individuals with different presentations of AUD. Studies have taken several approaches towards personalized treatments, such as pharmacogenetics, sex differences, family history, severity of alcohol withdrawal, drinking phenotypes, and biobehavioral markers [283, 289–293]. However, even these efforts may be overly simplistic given the complex nature of AUD. It is likely that personalized treatment approaches will need to account for multiple factors to truly tailor treatments to individual patients [294]. Conversely, the public health significance of the improved efficacy of AUD pharmacotherapy with clinically accessible phenotypes argue for wider dissemination and implementation of precision treatment recommendations identified to date.

A final issue to consider is the need to develop treatments for individuals with AUD and comorbid psychiatric disorders and for individuals with AUD and AALD. AUD often co-occurs with other psychiatric disorders, including other substance use disorders, personality disorders, major depressive disorder, anxiety disorders, and PTSD [295]. The development of integrated treatments, including combined behavioral and pharmacological interventions, which simultaneously address AUD and other co-occurring disorders, is difficult due to the complexity of treating multiple disorders and the limited understanding of the underlying mechanisms. However, this is a necessary area of research given the high rates of comorbidity in the AUD population. Treatment options for individuals with AALD are limited; of the FDA-approved medications, only acamprosate can be used without concerns of hepatotoxicity [296]. Of the non-FDA medications that may prove useful in this population, only baclofen has been evaluated in an RCT [94]. There is a clear need to develop additional treatments for this population.

4 Conclusions

In conclusion, the three widely approved medications for AUD (i.e., disulfiram, acamprosate, and naltrexone) are both modestly effective and underutilized. The heterogeneity inherent in AUD also presents the issue that no one medication is likely to be effective for all individuals with AUD. Therefore, it is necessary to develop more effective, novel, and diverse pharmacotherapy options and to improve access to treatment. The repurposed and novel medications reviewed in this article demonstrate promise for the future of AUD treatment. Additionally, the future directions indicated above offer potential improvements toward the advancement of precision medicine and personalized treatment for the heterogeneous AUD population.

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