Review

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Pharmacogenomics

Pharmacotherapies and personalized medicine for alcohol use disorder: a review

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Alcohol use disorder (AUD) is highly prevalent and among the leading causes of morbidity and mortality in the United States. Pharmacotherapies for AUD are limited, thus making identification of patient subgroups that are most likely to respond favorably crucial. In this article, pharmacogenetic research on US FDA-approved and commonly prescribed off-label medications for the treatment of AUD is comprehensively reviewed. While the field has advanced in understanding pharmacotherapies for AUD and potential genetic moderators of treatment responses, the pharmacogenetic data to guide the prescribing clinician are limited and should be interpreted with caution. Precision medicine for AUD with more beneficial treatment responses and minimal side effects remains a high priority for further research.

First draft submitted: 6 June 2020; Accepted for publication: 31 July 2020; Published online: 18 August 2020

Keywords: alcohol dependence • alcohol use disorder • genetics • epigenetics • personalized medicine • precision medicine • pharmacotherapy • problematic drinking • psychiatric comorbidity • treatment response

Alcohol use disorder (AUD) is a highly prevalent, chronic condition with a lifetime prevalence of 29% and a 12-month prevalence ranging from 5 to 14% [1–3]. Despite the high occurrence of AUD in the United States (U.S.) and its associated high cost to society, only an estimated 20–25% of individuals with AUD seek treatment [2,4], and of those only a fraction are prescribed medications used for promoting abstinence or reducing heavy drinking [5,6].

The US FDA has approved three oral medications for the treatment of AUD: disulfiram, acamprosate and naltrexone, as well as an injectable version of naltrexone. There are several drugs that are used off-label to treat AUD, including topiramate, gabapentin, baclofen, ondansetron and varenicline, among others [7]. Overall, the efficacy of these medications is limited and none of them systematically exhibit superior treatment response compared with placebo [8,9], with the possible exception of topiramate [10,11]. In fact, reviews of randomized double-blind placebo-controlled trials (RCTs) of naltrexone and acamprosate, arguably two of the most efficacious pharmacotherapies, show that roughly 40–70% of individuals taking either of these medications fail to respond positively [12–14]. Furthermore, treatment response is heterogeneous and multiple variables contribute to drug response rates, including clinical, environmental, genetic and social factors. Patients can show various clinical responses and side effects to the same drug, even at the same dose, with some responding well to one treatment but not another. This article is an updated review on the pharmacogenetic aspects of medications used to treat individuals with AUD [15].

Pharmacogenetics & personalized medicine

Pharmacogenetics refers to how genetic variation among patients can influence the pharmacokinetic and pharmacodynamic processes of a given drug and thus treatment response and adverse events. Pharmacokinetics refers to the absorption, distribution, metabolism and excretion of a drug. Pharmacodynamic studies focus on the effects of the drug on the body, such as how the drug interacts with receptors, transporters and downstream targets. Understanding these processes, particularly from a genetic basis, allows clinicians to utilize a medication with greater certainty of effectiveness by helping them predict a patient's optimal therapeutic response to a particular drug and limit side effects based on his or her unique genetic makeup.

Despite strong evidence for a genetic role in AUD, with heritability estimates between 50 and 60% [16–20], the degree to which genetic variants can influence individual differences in treatment response remains elusive [8]. Similar to the complex phenotype of AUD, for which a multitude of genes might play a role, drug response can also be considered a complex phenotype, with multiple genes likely contributing to the efficacy and side effect profile of a given drug [21]. As such, pharmacogenetics of AUD faces similar limitations, mainly underpowered sample sizes, largely due to the limited clinical trial sizes, which were not designed to answer pharmacogenetic questions. With this in mind, all presented findings should be interpreted with caution and require careful replications. While other fields, such as oncology, cardiovascular disease and diabetes, are making substantial progress in the direction of personalized medicine, several attempts have also been made into understanding the pharmacotherapy of AUD.

Disulfiram

In 1949, disulfiram became the first FDA-approved medication for the treatment of AUD [22]. However, it has limited clinical utility [23] and up to 80% of patients discontinue disulfiram treatment [24]. Disulfiram disrupts the metabolism of alcohol and causes 'acetaldehyde syndrome' by inhibiting the ALDH enzyme and increasing the presence of acetaldehyde, a toxic metabolite of alcohol, in the body [25]. When consumed with alcohol, disulfiram can produce adverse symptoms such as flushing, rash, tachycardia, hypertension, headaches, nausea, vomiting and diarrhea. These symptoms typically begin 5–15 min after alcohol consumption and subside anywhere from 30 min to a couple of hours after alcohol intake has stopped [26].

The main clinical effectiveness of disulfiram is due to an aversive reaction that reduces the urge to drink; however, efficacy reports have been inconsistent. A meta-analysis of open-label drug trials showed that disulfiram was superior compared with other active treatment groups [27] but this effect could not be shown in blinded trials. Strikingly, the authors reported that in double-blind RCTs there was no benefit of prescribing disulfiram for alcohol relapse prevention but reported significantly increased adverse events compared with controls [27]. One hypothesis of the reported effectiveness of disulfiram is thought to be a psychological effect of taking this medication and being aware of a potential aversive reaction [28], which might help explain open-label study findings and clinical reports.

Pharmacogenetics of disulfiram

Because of disulfiram's limited clinical utility, there have been only a few studies looking at pharmacogenetic effects on treatment response. Based on disulfiram's inhibition of the DBH enzyme, an enzyme implicated in AUD [29], one study investigated genetic variation in the *DBH* gene and treatment response to disulfiram [30]. The functional SNP rs1611115 (C-1021T) in the *DBH* gene was investigated [29] in a sample of 66 participants recruited from a specialized disulfiram outpatient clinic. Results showed no association between genotype and disulfiram treatment response but did demonstrate that T-allele carriers had an increased risk of adverse events when taking disulfiram [30]. Arias *et al.* [31] genotyped 107 European Americans with AUD and a comorbid axis I disorder for *OPRM1* rs1799971 and *DBH* rs1611115 and assigned them to receive naltrexone, placebo, disulfiram + placebo or naltrexone + placebo to investigate pharmacogenetic interactions. Results showed that the *DBH* genotype interacted significantly with disulfiram, such that homozygous C-allele carriers had a significant reduction in the number of drinks per drinking day compared with T-allele carriers on disulfiram.

A study that examined the effect of the null *ALDH2* allele on drinking outcomes in 109 Japanese men with AUD who were treated with disulfiram or placebo for an extended period of time (up to 26 weeks) found that individuals with this genotype had a better treatment response to disulfiram compared with placebo [32]. However, the sample was very small, with only 15 participants having the nonfunctional *ALDH2* allele.

In summary, there are only a few pharmacogenetic studies examining disulfiram, all limited by small-sample sizes. Changing clinical prescribing patterns of this drug based on individuals' genotypes is unjustified and larger, prospective studies are needed. In addition, safety concerns of consuming alcohol while taking this medication should be thoroughly explained to all individuals considering disulfiram as a treatment.

Naltrexone

The FDA approved naltrexone in 1994 for the treatment of AUD following independent clinical trials showing that it reduced craving and relapse rates in individuals with AUD [33,34]. The main mechanism of action is thought to be μ-opioid receptor antagonism that reduces alcohol's reinforcing effects and cravings [8,35]. One pivotal study documenting the efficacy of naltrexone for the treatment of AUD is the COMBINE study, a multisite RCT funded by the National Institute on Alcohol Abuse and Alcoholism [35,36]. This clinical trial demonstrated that individuals

with AUD who were administered daily oral naltrexone were more likely to have a higher percentage of days abstinent from alcohol and a longer time to first heavy drinking episode than patients treated with behavioral therapies, placebo, acamprosate or a combination of therapies. Interestingly, receiving daily naltrexone plus daily acamprosate did not result in an increased treatment benefit over taking naltrexone alone [36].

A meta-analysis comparing naltrexone to acamprosate with regard to heavy drinking and cravings showed superiority for naltrexone [37]. Furthermore, this clinical study mandated abstinence before the trial start date, and naltrexone exhibited larger effect sizes than placebo for maintenance of abstinence and reduction of heavy drinking.

Although several clinical trials have shown efficacy of naltrexone (for reviews, see 38,39), other studies have reported negative findings [40,41]. Notably, the randomized double-blind placebo-controlled Veterans Affairs Cooperative Study showed that there was no significant difference in time to first relapse among alcohol-dependent men treated with daily naltrexone or placebo [42].

One alternative option to daily naltrexone treatment is targeted naltrexone use. This dosing strategy involves taking naltrexone in anticipation of a potential high-risk drinking situation and has been shown to be an efficacious way for patients to reduce their heavy drinking behavior and to stay within healthier limits. In a 12-week trial by Kranzler *et al.* [43], 163 problem drinkers were randomly assigned to four groups: daily placebo, daily naltrexone, targeted placebo and targeted naltrexone. Results showed that men in the targeted naltrexone group had significantly lower mean drinks per day than men and women in the other groups. In addition, the targeted naltrexone group had significantly fewer drinks per drinking day compared with other groups. This approach represents an alternative to daily oral naltrexone for heavy drinkers who might wish to reduce their levels of alcohol consumption.

Pharmacogenetics of naltrexone

Due to the demonstrated efficacy of naltrexone [13,36,44,45], most pharmacogenetic studies have focused on the medication's main target, the μ-opioid receptor gene (*OPRM1*). One particular functional genetic variant in the *OPRM1* gene, rs1799971 (A118G), has been widely examined as it encodes an asparagine to aspartate substitution (Asn40Asp). Oslin *et al.* [46] demonstrated that the Asn40Asp polymorphism was significantly associated with relapse rates in individuals with AUD of European descent and naltrexone-treated patients with at least one copy of the Asp40 genetic variant were less likely to relapse to heavy drinking than naltrexone-treated patients who were homozygous for the Asn40 variant. There was no genotype effect on relapse rates in the placebo group but individuals treated with naltrexone who had the Asp40 allele reported longer times to first relapse than their Asn40Asn counterparts. Subsequent analysis of the COMBINE clinical data showed that individuals with the Asp40 allele who received naltrexone had a lower percentage of heavy drinking days and a higher percentage of days abstinent from alcohol than naltrexone-treated individuals with the Asn40Asn variant or either placebo group [47]. Furthermore, a haplotype-based approach suggested that Asn40Asp was the single locus in *OPRM1* that was predictive of naltrexone response in the COMBINE sample [48]. Kranzler *et al.* [49] showed that Asp40-allele carriers treated with naltrexone were also more likely to reduce nighttime drinking after having reported a greater desire to drink in the evening than Asn40Asn individuals. Another study showed that heavy drinkers with the 118G (Asp40) allele who were treated with naltrexone were significantly more likely to have nonhazardous drinking patterns compared with patients given placebo or 118A (Asn40) homozygous individuals in either the drug or the placebo group [50].

Additionally, a recent mobile health trial of naltrexone in 58 treatment-seeking individuals with AUD evaluated moderation effects of the *OPRM1* Asn40Asp genotype on associations between daily medication adherence and self-reported alcohol consumption and craving [51]. Results revealed a significant association between daily naltrexone adherence and reduced same-day alcohol consumption in Asp40-allele carriers, but not in Asn40 homozygotes.

However, other studies have not been able to reproduce these gene–treatment interactions. Using the Veterans Affairs Cooperative Study [42] sample, Gelernter *et al.* [52] failed to document an association between Asn40Asp genetic variation and rate of relapse and time to relapse among naltrexone-treated or placebo-treated males with AUD. Nevertheless, it is important to keep in mind that the original study was unable to demonstrate a treatment response difference between naltrexone and placebo in this sample [42]. Several other studies have shown that there were no significant differences in rates of abstinence [53] or drinking reduction between genetic groups [54]. Oslin *et al.* [55] conducted a prospective 12-week, double-blind placebo-controlled pharmacogenetic study of naltrexone in individuals with AUD. Participants were randomly divided into treatment groups based on genotype (Asp40 carriers vs Asn40 homozygotes) and treatment response was measured by relapse to heavy drinking. This study also could not find a significant interaction between *OPRM1* genotype and treatment condition, suggesting that the

Asp40 allele has no moderating effect on individual response to naltrexone treatment. However, limitations include that this study failed to document a significant treatment efficacy of naltrexone over placebo, making it difficult to assess the failure to replicate prior *OPRM1* genotype effects. Another prospective double-blind pharmacogenetic RCT of naltrexone in 152 individuals with AUD found a significant treatment effect of naltrexone over placebo, but no moderating effect of the *OPRM1* genotype [56]. Interestingly, the effect size (Cohen's d) for the naltrexone-placebo difference was much larger in Asp40-allele carriers compared with Asn40 homozygotes (1.1 vs 0.19) and they returned to heavy drinking at an increased trajectory compared with the other groups.

Two prospective 12-week studies investigated the relationship between the *OPRM1* genotype and response to open-label naltrexone treatment. The first study demonstrated a treatment effect of naltrexone over placebo on a number of drinking-related outcomes and craving, but did not find a moderating effect of the *OPRM1* genotype in a sample of 100 Australian individuals with AUD [57]. The second study examined 63 Koreans with AUD and showed that Asp40-allele carriers treated with naltrexone had an increased time to relapse compared with Asn40 homozygotes. Furthermore, although not statistically significant, individuals homozygous for the Asn40 allele had a 10.6-times greater relapse risk than Asp40-allele carriers [58]. However, it should be noted that there was no placebo control group and that analyses were conducted on a subset of medication-adherent patients, which, along with the resulting small sample size (n = 32), might have affected these results.

To date, only two studies have investigated pharmacogenetic moderators of naltrexone in comorbid populations. One study (described above) investigated interactions between functional genetic variants in genes associated with the mechanism of action of both naltrexone (i.e., *OPRM1* rs1799971) and disulfiram (i.e., *DBH* rs1611115) [31] in individuals with AUD and comorbid axis I diagnoses. They did not find significant moderating effects of the *OPRM1* SNP; however, they did reveal an interaction between *DBH* genotype and naltrexone, such that carriers of the T-allele showed a greater reduction in heavy drinking days compared with C-allele homozygotes on naltrexone. Another study investigated the *OPRM1* genotype in 108 individuals with AUD and depression who were assigned to naltrexone + placebo or naltrexone + citalopram and found no differences on any drinking-related outcomes [59].

Human laboratory models have also been used to investigate the degree to which SNPs in opioid receptor genes contribute to individual differences in responses to naltrexone and findings have been mixed. In one within-subject, double-blind laboratory study, 87 nontreatment-seeking heavy drinkers of east Asian descent completed an alcohol self-administration task after 5 days of naltrexone or placebo [60]. Results showed no significant moderating effects of *OPRM1* genotype on any outcome measure, which was in line with prior laboratory studies [54,61]. Another study administered naltrexone or placebo for 10 days followed by a cue reactivity task in nontreatment-seeking heavy drinkers and found that naltrexone increased alcohol urges in *OPRM1* Asp40-allele carriers but not in Asn40-allele homozygotes [62]. In contrast, Setiawan *et al.* [63] administered naltrexone or placebo for 6 days followed by an alcohol self-administration paradigm and found that naltrexone decreased alcohol-induced euphoria in female *OPRM1* Asp40-allele carriers. Similarly, another human laboratory study used a within-subject, double-blind, placebo-controlled design to investigate *OPRM1*-naltrexone interactions during an intravenous alcohol challenge session in 40 heavy drinkers [64]. They found that Asp40-allele carriers reported lower levels of craving and greater levels of alcohol-induced high across different breath alcohol levels. Furthermore, the blunting of alcohol-induced high after naltrexone treatment compared with placebo was greater in carriers of at least one Asp40 allele. A secondary analysis of this laboratory alcohol challenge examined potential moderating effects of genes encoding other targets of naltrexone, specifically, SNPs in the k- (*OPRK1* rs997917) and δ- (*OPRD1* rs4654327) opioid receptor genes on subjective responses to alcohol [65]. They found that self-reported alcohol sedation was lower in homozygous carriers of the *OPRK1* T-allele after treatment with naltrexone compared with carriers of the C-allele. Additionally, blunting of alcohol stimulation and craving was greater in *OPRD1* A-allele carriers than in *OPRD1* G-allele homozygotes after naltrexone treatment. These findings, however, are limited by the small-sample size and contradict null findings on these genetic variants in an earlier study [52], indicating that more research in larger-sample sizes is needed to clarify the role of the opioid receptor system in individual differences in naltrexone responses.

Overall, findings on potential pharmacogenetic effects of genetic variation in opioid receptor genes in clinical trials and human laboratory models have been mixed and a recent meta-analysis could not confirm an effect of *OPRM1* rs1799971 (A118G/Asn40Asp) on treatment response to naltrexone in AUD or heavy drinkers [66]. In summary, data support a small effect of naltrexone for the treatment of AUD; however, it remains unclear to what degree this effect is moderated by genetic variation in the *OPRK1, OPRD1* and *OPRM1* genes. Due to inconsistencies and lack of reliable large-scale prospective pharmacogenetic clinical trials, it is not suggested at this

point to include genotyping of opioid receptor genes in clinical decision-making for the treatment of individuals with AUD.

Injectable naltrexone

Medication adherence and treatment compliance to oral dosing is a concern in particular for individuals with a substance use disorder, such as AUD [67]. One available alternative to oral naltrexone is a long-acting intramuscular formulation, which was approved in 2006 by the FDA for the treatment of AUD. Advantages of long-acting intramuscular naltrexone is the release of active drug over the span of 4 weeks, thus potentially reducing some of the dose-related side effects seen with oral naltrexone while concurrently maintaining therapeutic plasma levels for the duration of the injection interval [68]. In addition, due to the infrequency of injections (only once a month), there are potential benefits of increasing compliance among AUD populations, ultimately increasing the beneficial treatment response [69]. Nethertheless, injection site-related side effects, such as necrosis, infection or inflammation, can occur, and the drug is contraindicated in individuals who take opioid analgesics [70].

Johnson *et al.* [71] showed in a double-blind RCT that injectable naltrexone was more efficacious than placebo in decreasing percentage of heavy drinking days in individuals with AUD. While both groups demonstrated a decrease in heavy drinking during the study, it should be noted that there was an unbalanced cell design, with 25 individuals receiving a naltrexone injection and only five receiving placebo. Injectable naltrexone was well-tolerated, and side effects included injection-site pain, headaches, nausea and abdominal pain. A subsequent, study by Garbutt *et al.* [72] examined treatment response to injectable naltrexone among alcohol-dependent individuals over a 6-month period. In this study, participants were divided into four groups: 380 mg of long-acting naltrexone injection, 190 mg of long-acting naltrexone injection and matching-volume placebo injections respectively. Results of monthly naltrexone injections showed that both doses of long-acting naltrexone injections reduced heavy drinking compared with placebo, but only the 380-mg dose offered a significant reduction in heavy drinking over placebo. However, dose-related adverse events emerged in particular for the 380-mg group, including nausea, injection-site pain, fatigue, dizziness and decreased appetite, compared with the low-dose naltrexone group and both placebo groups. Subsequent gender analysis appeared to support efficacy for decreasing drinking in particular for men for the high-dose naltrexone group. Women in the high-dose group actually reported an increase in drinking. Another study retrospectively compared 32 veterans with AUD who had been treated with oral or long-acting injectable naltrexone [73]. Results showed that median time to relapse was significantly longer in patients treated with injectable compared with oral naltrexone.

A follow-up analysis of the Garbutt *et al.* [72] study revealed additional findings pertaining to the efficacy of injectable naltrexone for individuals who reported 4 or more days of abstinence prior to treatment. Here, high-dose naltrexone treatment resulted in an increased rate of complete abstinence for the entirety of the trial compared with placebo [74]. High-dose naltrexone patients also reported an increased time to first drink and first heavy drinking episode and a lower number of drinking days and heavy drinking days per month compared with the placebo group.

Clinically, injectable naltrexone appears to be well-tolerated, easy to administer, more likely to increase compliance in patients and efficacious for men. Additionally, benefits of injectable naltrexone include the reduction of oral prescribed medications [70,75].

Pharmacogenetics of injectable naltrexone

There are currently no pharmacogenetic studies of injectable naltrexone in AUD populations.

Acamprosate

Although the exact mechanisms of action of acamprosate are not fully understood, there is evidence acamprosate counteracts alcohol-induced glutamate hyperactivation by exerting antagonistic effects on N-methyl-D-aspartic acid receptors while indirectly affecting γ-aminobutyric acid type A ($GABA_A$) neurotransmission [76]. Acamprosate received FDA approval in 2004 for AUD treatment through preventing relapse and promoting abstinence [77]. Clinically, it appears to have utility for patients seeking to remain abstinent as opposed to reducing their drinking levels [45]. Common side effects of this drug typically include diarrhea, dizziness and headaches [26].

The first US study of acamprosate's efficacy in AUD initially reported that the percentage of days abstinent from alcohol was not significantly different between acamprosate-treated AUD patients and patients receiving placebo. However, a secondary analysis of this study documented that acamprosate was more effective than placebo

in patients who had an initial goal of abstinence [78]. A 2008 report on the efficacy of acamprosate examined results from three European double-blind RCTs and found that complete abstinence from alcohol was significantly higher in alcohol-dependent patients treated with acamprosate than in patients treated with placebo. Furthermore, individuals taking acamprosate reported a longer time to first drink than those receiving placebo [77]. A 2010 meta-analysis looked at 17 clinical trials and determined that acamprosate significantly increased continuous abstinence compared with placebo [14] and was well tolerated and effective in reducing risk of drinking following detoxification in alcohol-dependent individuals. Other meta-analyses comparing naltrexone and acamprosate found that acamprosate was more efficacious than naltrexone in maintaining abstinence [37,79]. Additionally, acamprosate demonstrated larger effect sizes than placebo on measures of abstinence in individuals who were detoxified prior to medication administration [37,38].

As with other medication for the treatment of AUD, there have been also negative studies indicating no benefit of treatment with acamprosate. The COMBINE study (discussed above) compared treatment response to naltrexone, acamprosate, placebo, behavioral therapies or a combination of therapies in individuals with AUD. The findings did not support the efficacy of acamprosate in the treatment of AUD [36]. Additionally, an Australian RCT by Morley *et al.* [80] and a German RCT by Mann *et al.* [81] failed to find a significant effect of acamprosate on time to first drink, time to relapse and continued abstinence.

Pharmacogenetics of acamprosate

One candidate gene that has been studied in relation to acamprosate treatment is the *GATA4* gene. *GATA4* encodes GATA4-binding protein type 4, a transcription factor that regulates the expression of atrial natriuretic peptide (ANP) [82]. The intronic SNP rs13273672 was associated with AUD [83,84], although other studies did not confirm this association [85,86]. It has been suggested that reduced ANP expression in the CNS is associated with the dysregulation of stress and anxiety mechanisms in the brain, a possible link between ANP and AUD [87]. In a randomized, double-blind, placebo-controlled study, Kiefer *et al.* [88] showed that alcohol-dependent individuals with the rs13273672 G allele were more likely to have decreased time to relapse following acamprosate treatment than alcohol-dependent individuals with the AA genotype. This genetic effect was not seen in patients treated with naltrexone or placebo.

Acamprosate clinical efficacy on alcohol craving has been linked to polymorphisms in genes involved in positive and negative reinforcement systems, including the dopamine receptor and the $GABA_A$ receptor, respectively. In *DRD2 A1A1-, GABRA6 1519 C-* and *GABRB2 1412TT*-allele carriers, acamprosate outperformed naltrexone in reducing alcohol craving, as measured by a visual analog scale and physiological assessments before and after cue exposure [89]. Genetic variants in *GRIN2B*, the gene that encodes the GluN2B subunit of *N*-methyl-d-aspartic acid receptors, have been found to be associated with length of abstinence following acamprosate treatment [90]. In the discovery sample of this study, 225 alcohol-dependent participants were administered acamprosate for 3 months in an open-label trial. To replicate the initial findings, a replication sample of 110 alcohol-dependent men treated with acamprosate from the PREDICT study was used [91]. Genetic analyses from the discovery sample showed that the minor allele (A) of SNP rs2058878 in *GRIN2B* was associated with a longer period of abstinence. Interestingly, in the replication sample, this association was marginally significant. Additionally, the minor allele (G) of rs2300272, an SNP in high-linkage disequilibrium with rs2058878, was found to be significantly associated with a shorter abstinence period in the independent replication sample. Although these findings suggest a relationship between genetic variation in *GRIN2B* and response to acamprosate, it should be noted that interpretations of these data are limited due to the fact that this study did not use a placebo arm [90].

In summary, data suggest that acamprosate could be clinically effective for patients who have an initial desire to remain abstinent. Acamprosate treatment efficacy may be partially moderated by genetic variation of genes regulating stress and reward pathways, including *GATA4*, *DRD2*, *GABRA6*, *GABRB2* and *GRIN2B*.

Topiramate

Topiramate is an anticonvulsant medication [92] that increases the transmission of gamma-aminobutyric acid (GABA) and inhibits the transmission of glutamate [93]. The drug is not currently FDA-approved for the treatment of AUD, but clinically it is prescribed off-label. Despite its off-label clinical use, an estimated 20% of patients taking topiramate have dropped out of AUD-related clinical trials of this drug due to its side effects [94].

Topiramate's clinical efficacy for AUD treatment has been demonstrated in several studies. Johnson *et al.* [95] documented in a 12-week double-blind RCT that topiramate-treated individuals with AUD reduced drinks per

day on average, reduced drinks per drinking day on average and decreased the percentage of heavy drinking days compared with the placebo group. Side effects of topiramate treatment included dizziness, paresthesia, weight loss, concentration and memory difficulties, and psychomotor slowing. A subsequent 14-week double-blind RCT of topiramate demonstrated that patients with AUD receiving the drug were significantly more likely to have a decreased percentage of heavy drinking days than the placebo group. The topiramate group additionally reported more days abstinent from alcohol and fewer drinks per drinking day compared with the placebo group. However, individuals receiving topiramate had significantly greater reports of the following side effects: paresthesia, taste perversion, anorexia, difficulty with concentration/attention, nervousness, dizziness and pruritus [94]. In a laboratory study [96], 61 heavy drinkers received topiramate (200 or 300 mg) or placebo. Medication dosage was reached after a 32-day titration period and maintained for 1 week. Both topiramate groups reported significantly lower rates of drinking and heavy drinking during the titration period. A recent, comprehensive meta-analysis of seven RCTs showed that topiramate is significantly better than placebo in both decreasing aggregate measures of heavy drinking days and increasing aggregate measures of abstinence for alcohol-dependent patients. However, the overall effect of this drug is moderate. Several studies further showed that on measures of abstinence, heavy drinking and craving, topiramate demonstrated larger effect sizes than both naltrexone and acamprosate, suggesting that further investigation into the efficacy of topiramate is warranted [10,11,97].

De Sousa *et al.* [98] compared disulfiram with topiramate in an open-label study and showed that disulfiram is more efficacious than topiramate at preventing relapse and increasing time to first relapse in participants with AUD. Limitations of this unblind study include that it was an all male sample and that there was no placebo group [99]. A 12-week RCT of 106 patients with AUD found there was no significant difference between topiramtae and placebo groups on percentage of heavy drinking days and time to first day of heavy drinking, though the patients were enrolled in a residential treatment program of alcohol detoxification, so the intensive psychosocial interventions may have eclipsed topimarate's effect in reducing alcohol consumption [100]. Another RCT involving 170 subjects with both cocaine and AUD found that topiramate did not have greater efficacy over placebo in reducing alcohol or cocaine use, but it was superior at reducing alcohol craving [101]. While some clinical trials found that topiramate was not effective in reducing alcohol consumption, these studies were done in specific patient populations and may not be generalizable.

Pharmacogenetics of topiramate

One way topiramate may reduce glutamate transmission is through antagonizing AMPA/kainate glutamate receptors containing the GluK1 subunit, which is encoded by the *GRIK1* gene [102,103]. Pharmacogenetic studies of topiramate have focused on an intronic SNP (rs2832407) in the *GRIK1* gene due to previous data demonstrating an association between *GRIK1* and AUD [102]. A placebo-controlled 12-week study of 138 heavy drinkers demonstrated that topiramate significantly decreased heavy drinking days and increased days abstinent from alcohol compared with placebo. Among European Americans (n = 122 subsample), only the topiramate-treated individuals who were C-allele homozyguos for SNP rs2832407 showed a significant decrease in heavy drinking days relative to placebo [104]. A replication and extension study of these findings further showed the association between genetic variation in the *GRIK1* gene and topiramate response. Kranzler *et al.* [105] not only confirmed their initial findings but also showed that rs2832407*C homozygous individuals treated with topiramate reported a decrease in positive alcohol expectancies and desire to drink, an effect that was not seen in A-allele carriers. A study in nontreatment-seeking heavy drinkers examined the effect of genotype on the severity of side effects of topiramate [106]. Results showed a significant interaction between genetic variation of SNP rs2832407 and medication, such that A-allele individuals treated with topiramate reported higher side effect severity in comparison to participants with the CC genotype receiving topiramate.

In summary, there is emerging evidence that topiramate has efficacy in treating AUD, and one meta-analysis has shown that it has larger effect sizes than both naltrexone and acamprosate. Side effects can be concerning and limit clinical use. From a pharmacogenetic perspective, there is evidence that C-allele homozygous individuals for SNP rs2832407 in *GRIK1* are not only more likely to respond beneficially to topiramate than their A-allele counterparts but also experience a lower rate of side effects when receiving topiramate. These findings suggest that this SNP moderates treatment efficacy of topiramate. Clinically, this medication should be prescribed with caution and a close monitoring of potential side effects.

Gabapentin

Gabapentin is an oral anticonvulsant drug that is FDA-approved for the treatment of epilepsy, restless leg syndrome and postherpetic neuralgia, with respective dosages ranging from 300 to 1800 mg per day [107–109]. While its exact therapeutic mechanisms remain unclear, data from preclinical and clinical studies indicate that they include the selective inhibition of voltage-gated calcium channels containing the α2δ-1 subunit, the enhancement of voltage-gated potassium channels, as well as the modulation of GABA activity [110]. In recent years, gabapentin has been prescribed off-label to treat AUD-related withdrawal, cravings and insomnia. While data from well-controlled clinical trials of gabapentin are still limited, there is some evidence that it might be more efficacious than placebo at improving drinking-related outcomes in AUD populations. A 2015 review by Leung *et al.* [111] reported on three RCTs investigating the effect of gabapentin on drinking outcomes in AUD [112–114] and five prospective studies of its effects on alcohol withdrawal [115–119]. Data from the three RCTs (total n = 231) showed significant dose-dependent effects of gabapentin compared with placebo on the number of abstinent days, reductions in heavy drinking and increased time to first heavy drinking day, with a favorable safety profile. Recently, Kranzler *et al.* [120] combined previously reviewed RCTs with three newly published [121–123] and one additional prior RCT [124] in a meta-analysis of gabapentin's efficacy for the treatment of AUDs (total n = 482). Results indicated a medium-sized effect of gabapentin over placebo on the percentage of heavy drinking days; however, effects on other outcomes, including abstinence, relapse to heavy drinking, abstinent days, number of drinks per day and gamma-glutamyl transferase concentration, were not significant. While no serious adverse events were reported in any of the above-mentioned AUD RCTs, adverse events associated with gabapentin use have been reported, particularly at higher dosages, including dizziness, somnolence and peripheral edema [125]. It should be noted that a systematic review has found misuse of gabapentin for recreational purposes, self-medication or self-harm, either alone or combined with other substances, such as alcohol or opioids, in 1% of the general population and 15–22% of individuals who abuse opioids [126].

In conclusion, given the limited number of double-blind RCTs in AUD and the reported risk of misuse of gabapentin, particularly in substance use disorder populations, its use as a first-line treatment for AUD is not recommended at this time.

Pharmacogenetics of gabapentin

There are currently no pharmacogenetic studies of gabapentin in AUD.

Baclofen

Baclofen is a $GABA_B$ receptor agonist used as a skeletal muscle relaxant. Although it is not currently FDA-approved to treat AUD, it is being considered as a second-line pharmacotherapy and is clinically prescribed off-label. Baclofen has several potential mechanisms of action in AUD. Primarily, it is presumed that baclofen reduces the reward pathway of alcohol by activating $GABA_B$ receptors in the mesolimbic circuit and ventral tegmental area to suppress alcohol-stimulated dopamine release [127–130].

Case reports have shown that baclofen helped patients reduce alcohol intake and maintain abstinence, as well as relieve cravings and anxiety related to AUD [131–134]. However, RCTs revealed conflicting results and several have found no effect of baclofen on AUD. A meta-analysis of 12 RCTs comparing baclofen with placebo found that baclofen had a significant effect on abstinence rates [135] and a meta-analysis of 14 double-blind RCTs found a small, but not statistically significant, advantage of baclofen for the treatment of AUD [136]. However, there was no difference between baclofen and placebo for increasing the number of abstinent days or decreasing heavy drinking, craving and anxiety [128,135,136]. These studies also have limited external validity given the high heterogeneity among trials, small-sample sizes and exclusion of comorbidities. These RCTs provide no clear-cut evidence of the efficacy of baclofen in treating AUD and there is a need for longer-term controlled studies with larger sample populations.

Pharmacogenetics of baclofen

Given the high heterogeneity of responses to baclofen, Morley *et al.* examined the SNP (rs29220) in the $GABA_B$ receptor subunit 1 gene (*GABBR1*) of alcohol-dependent men and women to determine if the response to baclofen is moderated by this SNP. They found that C-allele homozygotes treated with baclofen had a longer time to relapse and more days abstinent compared with placebo or participants with one or two G-alleles treated with baclofen. There were no significant differences in the frequency of adverse events except for dizziness, with the G-genotype group reporting a higher frequency of dizziness compared with the CC group [137]. These findings begin to explain

some of the heterogeneity in response to baclofen treatment and may also be predictive of adverse events when using baclofen to treat AUD.

Ondansetron

Ondansetron is a 5-HT_3 receptor antagonist that is used as an antiemetic during chemotherapy and opioid treatment. It is not FDA-approved to treat AUD but has been shown to reduce drinking and promote abstinence. Early-onset AUD is associated with serotonergic abnormality and antisocial behaviors and placebo-controlled trials of low doses of ondansetron (4 mg/kg twice daily) have shown that it decreased alcohol consumption and alcohol-related problems and increased abstinence in patients with early-onset AUD [138,139].

Pharmacogenetics of ondansetron

Polymorphisms in the *SLC6A4* gene, which codes for the serotonin transporter (5-HTT), may modulate the severity of alcohol consumption and predict the therapeutic response of ondansetron. Two allelic variants in the *SLC6A4* gene have been shown to be associated with AUD. The *SLC6A4* promoter has a polymorphic region with a long form (L) and a short form (S) and these polymorphisms have been implicated in several psychiatric disorders, including AUD. The SNP rs1042173 (T/G) in the 3′-untranslated region of the *5-HTT* gene has also been reported to be associated with the severity of alcohol consumption. Johnson *et al.* found that alcohol-dependent individuals with the *5HTTLPR* LL or LL/TT combination genotypes who received ondansetron reported a lower number of drinks per day and a higher percentage of abstinent days than those who received placebo or than ondansetron-treated individuals with the other genotypes [140]. Additionally, Kenna *et al.* [141] randomly assigned 77 nontreatment-seeking individuals with AUD to receive sertraline or ondansetron for 3 weeks, followed by placebo for 3 weeks and the alternate drug for 3 weeks. Each medication period was followed by a laboratory alcohol self-administration session and the assessment of alcohol consumption in the 7 days prior. Genotyping was used to match and mismatch *5HTTLPR* L-allele homozygotes and S-allele carriers to the treatments. There was a significant reduction in drinks per drinking day but not in the amount of alcohol consumed in the laboratory session after the first medication period in ondansetron-treated L-allele homozygotes. Furthermore, a secondary analysis of the above-described study [140] found that individuals with allelic variation in the *HTR3A* (rs1150226-AG and rs1176713-GG) and *HTR3BB* (rs17614942-AC) genes showed a significant difference between ondansetron and placebo in drinks per drinking day, percentage of heavy drinking days and percentages of days abstinent [142]. These findings may help clinicians create a genotype panel to be used to predict the outcome of treating AUD with ondansetron.

Varenicline

Varenicline is a partial α4β2 nicotinic acetylcholine receptor agonist used to help with smoking cessation. Although not FDA-approved to treat AUD, it is prescribed off-label and clinical trials offer promising results about its efficacy in reducing alcohol cravings and consumption. Varenicline is thought to reduce cravings and rewarding effects of cigarettes by partial binding to α4β2 nicotinic acetylcholine receptors to prevent full activation of these receptors and subsequent dopamine release by nicotine and may have a similar mechanism of action in alcohol reinforcement and craving [143].

In a double-blind, placebo-controlled Phase II trial of 200 smokers and nonsmokers with AUD, the varenicline group had a significantly lower percentage of heavy drinking days per week, drinks per day and alcohol craving compared with the placebo group [144]. Of interest, when participants were divided into subgroups, it was discovered that individuals who reduced their number of cigarettes per day saw a significant reduction in drinking with varenicline compared with those who did not change or who increased the amount they smoked. Other variables that significantly moderated varenicline efficacy were treatment drinking goal, years drinking regularly, age and depressive symptoms [145,146]. Two other Phase II studies showed that varenicline was effective at treating AUD in a population comorbid for smoking, with smoking abstinence rate significantly higher and mean drinks per drinking day significantly lower after varenicline treatment compared with placebo, with men in particular [147,148].

Other Phase II RCTs found that varenicline did not reduce the number of heavy drinking days or sustain abstinence, but it did reduce the daily amount of alcohol consumed, alcohol craving and levels of the alcohol marker phosphatidylethanol in the blood [149,150]. Although heavy drinking days were not reduced, other symptoms of AUD were decreased by varenicline and it may be a promising treatment option for AUD, especially in patients comorbid for smoking.

Pharmacogenetics of varenicline

There are currently no pharmacogenetic studies of varenicline in AUD.

Nalmefene

Nalmefene is an antagonist to the μ- and δ-opioid receptors and a partial agonist to the κ-opioid receptor [151]. Early double-blind placebo-controlled studies of different dosages of nalmefene found that it reduced relapse rates compared with placebo in individuals with AUD [152,153]. The most commonly reported side effects of nalmefene are temporary and occur at treatment initiation, including dizziness, insomnia, headache, vomiting, fatigue and somnolence [154]. In the European Union, nalmefene was approved by the EMA as a treatment for AUD, specifically, to help reduce alcohol consumption based on three studies [155–157]. However, this decision has been criticized as the supporting evidence was inconsistent, lacked *a priori* specified outcome measures and sensitivity analyses, defined patient groups retrospectively and did not use appropriate comparators [158]. One multisite 28-week RCT of targeted nalmefene [159] assigned 403 heavy drinkers to take placebo or 10–40 mg of nalmefene as needed (i.e., 'when they believed drinking to be imminent'). Individuals treated with nalmefene had fewer heavy drinking days and greater reductions in biomarkers of alcohol use, including serum alanine aminotransferase and gamma-glutamyl transferase, compared with those in the placebo condition.

An early meta-analysis of five published and unpublished nalmefene RCTs (total n = 2567) [160] showed weak associations with reductions in binge drinking at 1 and 6 months, as well as a reduction in total alcohol consumption at 6 months. However, these findings lacked robustness and did not hold when a more conservative approach to withdrawals was employed. A more recent meta-analysis of double-blind RCTs of nalmefene (n = 9), naltrexone (n = 14), topiramate (n = 4), acamprosate (n = 1) and baclofen (n = 4) in AUD [11] found that nalmefene had a small effect on total alcohol consumption and drinks per drinking day compared with placebo; however, no superiority of nalmefene against any of the other medications was found and none of the RCTs included provided direct comparisons to active treatments.

In conclusion, while nalmefene may have some efficacy in reducing alcohol consumption, there is not enough high-quality data to establish its value for the treatment of AUD. In the future, carefully designed, well-powered RCTs are needed to compare nalmefene not only to placebo but also to other approved pharmacological AUD treatments, such as naltrexone.

Pharmacogenetics of nalmefene

Research on pharmacogenetic effects of potential moderators of individuals' responses to nalmefene are limited to date. To the best of our knowledge, there has only been one study. Arias *et al.* [161] conducted a secondary analysis on a subsample of 272 participants of the above-described 28-week RCT of targeted nalmefene by Karhuvaara *et al.* (2007) and examined moderating effects of polymorphisms in a number of opioid receptor genes. No interactions between genetic variation in *OPRM1, OPRK1* or *OPRD1* and treatment response to nalmefene were found.

Selective serotonin reuptake inhibitors & serotonin-related drugs

Selective serotonin reuptake inhibitors (SSRIs) are widely prescribed for the treatment of depression and anxiety, but clinical trials examining the efficacy of SSRIs in treating comorbid AUD, depression and anxiety are limited and have shown some promising results [162–164]. The SSRI sertraline was studied in a 12-week RCT and demonstrated that in currently depressed alcohol-dependent patients, sertraline treatment was associated with individuals consuming fewer drinks per drinking day than individuals receiving placebo. However, there was no difference in other drinking measures between the two groups. Interestingly, female participants receiving sertraline reported fewer depressive symptoms than female participants taking placebo [165]. A later study by Kranzler *et al.* [166] reported no significant difference in either placebo or sertraline group measures of depression and AUD, with both groups showing a decrease in depressive symptoms and alcohol consumption.

Combination treatment of sertraline and naltrexone may provide more treatment benefits than monotherapy alone in individuals with AUD and depression. A study of 170 individuals with comorbid depression and AUD randomly assigned individuals into either a sertraline alone, naltrexone alone, naltrexone + sertraline or a double-placebo condition. The combination treatment group showed an increased rate of abstinence from alcohol and an increase in time to relapse to heavy drinking compared with other treatment groups. Furthermore, this group showed fewer depressive symptoms and fewer adverse events than other groups [167].

For the practitioner, there is evidence to suggest that combination (naltrexone + sertraline) pharmacotherapy is more promising for the treatment of co-occurring AUD and major depressive disorder than simply prescribing sertraline alone. However, female patients may see a reduction in symptoms while taking only sertraline.

There are only a few studies of SSRI pharmacotherapy for comorbid AUD and post-traumatic stress disorder (PTSD). One randomized, placebo-controlled study showed that sertraline-treated individuals with comorbid AUD and PTSD reported a significant reduction in drinks per drinking day compared with placebo, but only if they had early-onset PTSD and less severe AUD. Alternatively, placebo-treated individuals with more severe AUD and later-onset PTSD reported significantly fewer drinks per drinking day and a lower average number of alcoholic beverages per day. Sertraline may provide beneficial treatment for a subset of PTSD/alcohol-dependent individuals [168] but additional studies are needed. A later study into comorbid AUD/PTSD in veterans compared the efficacy of paroxetine (SSRI) to that of desipramine (norepinephrine reuptake inhibitor) in combination with naltrexone or placebo. Participants were divided into four groups: paroxetine + naltrexone, paroxetine + placebo, desipramine + naltrexone and desipramine + placebo. Paroxetine was not significantly more efficacious than desipramine in reducing PTSD symptoms, but desipramine reduced alcohol consumption compared with paroxetine. Interestingly, naltrexone did not reduce drinking outcomes, although it did reduce craving compared with placebo [169].

Several clinical trials have also looked at comorbid social anxiety and AUD. One double-blind RCT examined the efficacy of paroxetine for the treatment of these co-occurring disorders. In this study, paroxetine was significantly more efficacious than placebo at reducing anxiety symptoms [170], but there was no significant difference between the two treatments on number of drinks consumed or frequency of drinking [171].

A study by Tollefson *et al.* [172] examined comorbid AUDs and generalized anxiety disorder. In this double-blind RCT, they determined that buspirone, a serotonin partial agonist, was superior to placebo in reducing anxiety symptoms and the number of days the participants reported a desire to drink alcohol.

Pharmacogenetics of SSRIs & serotonin-related drugs

The serotonin transporter gene (*SLC6A4*) represents one of the most widely studies genes related to pharmacogenetics of antidepressant drugs [173–176]. Genetic variation in *SLC6A4* has been shown to be associated with numerous AUD phenotypes, including craving and drinking intensity [177–179]. In particular, one polymorphism in the promoter region of the gene (5-HT transporter gene-linked polymorphic region: 5-HTTLPR) includes an insertion or deletion of a repetitive sequence, producing a short allele (S) or a long (L) allele [180]. The long version of this *5-HTTLPR* has been shown to affect transporter function, resulting in higher serotonin reuptake by the transporter [180]. There is also an A/G SNP (rs25531) in the *5-HTTLPR* tightly linked to the L allele producing in effect a tri-allelic genotype (La, Lg and S) [181]. The Lg allele is similar in functionality to the S allele [182]. In a placebo-controlled trial of sertraline by Kranzler *et al.* [183], it was shown that age of onset of AUD and genetic variation of *5-HTTLPR* had moderating effects on sertraline efficacy. In a follow-up analysis, they examined the moderating effect of evening negative mood on nighttime consumption of alcohol. Their study demonstrated that placebo-treated individuals with early-onset AUD who were homozygous for the La allele reported less nighttime drinking after experiencing an increased level of anxiety during the day, implicating a moderating role of anxiety in pharmacogenetic outcomes [184]. In a within-subject, double-blind, placebo-controlled laboratory study, 77 individuals with AUD received sertraline or ondansetron, placebo and finally, the alternate drug for 3 weeks each [185]. After each 3-week period, participants completed an alcohol-self-administration paradigm in the laboratory. There were no significant pharmacogenetic effects for men. However, sertraline-treated *5-HTTLPR* S-allele-carrying women reported a significant reduction in drinks per drinking day compared with sertraline-treated women homozygous for the L allele. Furthermore, sertraline-treated women carrying the *5-HTTLPR* S allele and the *DRD4* <7-repeat allele reported significantly fewer drinks per drinking day in the 7-day period leading up to the alcohol self-administration session and consumed fewer drinks during the laboratory session.

Clinically, a single drug that offers beneficial treatment response for co-occurring AUD and depression and anxiety disorders does not currently exist. Although SSRIs have been studied for the treatment of these comorbid disorders, studies report conflicting results. Although there seems to be some genetic moderation of variation in *5-HTTLPR* on SSRI efficacy in anxious individuals with AUD, at this time these findings have not been replicated and offer little clinical utility.

Given the high rates of co-occurrence between AUD, major depressive disorder and anxiety disorders, there is an unmet clinical need to find medications that can safely and effectively treat one or both disorders, but also determine prior to prescription who will beneficially respond to which medication.

Discussion

AUD has a high prevalence rate and represents one of the leading causes of morbidity and mortality in the United States and globally. Given the significant individual and economic costs, and the limited number and efficacy of FDA-approved treatments for AUD, it is crucial to develop novel pharmacotherapies and identify patient subgroups that are most likely to respond favorably to existing treatments. In this review, we summarized pharmacogenetic research on FDA-approved and commonly prescribed off-label medications for the treatment of AUD. Although the field has made some progress in understanding and treating AUDs over the past few decades, limited data exist for the use of genetic and/or biomarker information to guide the prescribing clinician.

One of the main obstacles in the development of effective pharmacotherapies for AUD is the lack of standardized trial designs and outcome measures. Some studies determine treatment efficacy by the successful attainment of complete abstinence, while others report significant results if participants have simply reduced their total number of drinks per day from baseline. In an effort to direct future pharmacotherapy trials for the treatment of AUDs, the FDA released a draft of a guidance for industry entitled 'Alcoholism: Developing Drugs for Treatment' (www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation). According to the FDA, the goal of treatment is to permanently reduce the adverse physical and psychosocial effects of alcohol-related behavior, which is essentially a harm-reduction approach. However, long-term behavior modification is difficult to assess during a short RCT. Therefore, clinical medication trials should be designed in a way that demonstrates a current modification in drinking habits that will indicate future patterns that are healthier and safer. In light of this guidance, trials should allow a grace period for individuals to attain abstinence or reduce their drinking to below clearly defined heavy drinking levels. A treatment could then be deemed efficacious if individuals sustain these healthier drinking patterns for a minimum of 6 months as a result of this intervention. Ideally, standardizing outcome measures in this way will generate more consistent results pertaining to the efficacy of a given pharmacological intervention.

Another main factor for the lack of efficacious new medications for AUDs is the lack of development of safe and effective novel compounds specifically for use in AUD. While efforts have been made to examine off-label compounds, such as topiramate, ondansetron, baclofen, gabapentin and varenicline, no meaningful major *a priori* drug discovery efforts based on the distinct underlying neurobiology of AUDs exist. While research into efficacy of off-label drugs and repurposing drugs can be promising, additional efforts are needed. Innovative new drug developments should also include reverse translational strategies using genomic and epigenomic approaches as this can be a way of delivering new potential drug targets for AUD [186–189].

Furthermore, while pharmacogenetic studies discussed in this review have identified a number of promising genetic variants that might contribute to individual variability in treatment responses to existing AUD pharmacotherapies, their interpretation is methodologically limited. Many of the studies were conducted in small samples and did not correct for multiple comparisons, which may have resulted in the reporting of false-positive or false-negative results. It should also be noted that these studies included a very broad phenotype of alcohol use, from nontreatment-seeking heavy social drinkers to treatment-seeking individuals with severe AUD, which limits comparability across studies. In addition, while some of the studies' samples were limited to one gender [32], other studies with balanced samples found moderating effects of gender on treatment response to naltrexone, ondansetron and sertraline [43,72,185], suggesting the need for future studies to ensure balanced samples.

Another limitation of hitherto existing pharmacogenetic research is its primary focus on individuals with AUD of European ancestry and the lack of studies in ethnic minorities (for a review, see 190). There are significant differences in the prevalence of genetic variants, such as the *OPRM1* Asp40 allele, among populations of different ancestries. Therefore, potential-moderating effects of genetic variants, and consequently the effectiveness of pharmacotherapies, may vary by population. For example, an ethnic-specific meta-analysis [191] demonstrated that the *OPRM1* Asp40 allele was associated with an increased risk for AUD in individuals of Asian but not European ancestry. In fact, a recent, large (n = 28,000) meta-analysis by Schwantes-An *et al.* [192] found the *OPRM1* Asp40 allele to be modestly protective against substance use disorders in individuals of European ancestry. This underlines the clinical need for future pharmacogenetic research and large-scale RCTs to include underrepresented ethnic minorities. This increased inclusivity has the potential to advance our understanding of the mechanisms underlying genetic variants'

Table 1. Summary of clinical and pharmacogenetic studies of alcohol use disorder.

Drug	FDA approved for AUD	Clinical summary	Pharmacogenetics summary
Disulfiram	Yes	Disulfiram is an FDA approved, aversive AUD treatment and data on its clinical effectiveness in decreasing the urge to drink compared with other pharmacotherapy interventions or placebo have been inconsistent	There are only a small number of pharmacogenetic studies examining *DBH* and *ALDH2* genotypes' moderating effects on disulfiram, all of which were limited by small sample sizes; therefore, larger prospective studies are needed
Naltrexone	Yes	Naltrexone, a μ-opioid receptor antagonist, is the most widely studied FDA-approved AUD medication with demonstrated efficacy	Findings from pharmacogenetic studies have been mixed and it remains unclear to what degree the treatment effect is moderated by genetic variation in the *OPRK1*, *OPRD1* and *OPRM1* genes; therefore, reliable large-scale prospective pharmacogenetic clinical trials are needed
Injectable naltrexone	Yes	Injectable naltrexone is a long-acting intramuscular injectable form of naltrexone that appears to be well-tolerated, easy to administer, more likely to increase compliance in patients and efficacious for men	None
Acamprosate	Yes	Acamprosate is an FDA-approved AUD treatment with mixed findings on its efficacy for preventing relapse and promoting abstinence	Acamprosate treatment efficacy may be partially moderated by genetic variation of genes regulating stress and reward pathways, including *GATA4*, *DRD2*, *GABRA6*, *GABRB2* and *GRIN2B*
Topiramate	No	Topiramate is an anticonvulsant medication that is prescribed off-label to treat AUD. There is evidence that topiramate is more efficacious than placebo in treating AUD, and one meta-analysis has demonstrated that it has larger effect sizes than both naltrexone and acamprosate; however, an estimated 20% of patients taking topiramate have dropped out of AUD-related clinical trials of this drug due to its side effects	Data suggest that C-allele homozygous individuals for SNP rs2832407 in *GRIK1* are not only more likely to respond beneficially to topiramate than their A-allele counterparts but also experience a lower rate of side effects when receiving topiramate; however, this has not yet been replicated
Gabapentin	No	Gabapentin is an oral anticonvulsant medication that has been prescribed off-label to treat alcohol craving and withdrawal with a favorable safety profile. While there are a small number of clinical trials with data supporting the efficacy of gabapentin for some but not all drinking-related outcome measures, it should be noted that a systematic review has found a risk of misuse of gabapentin for recreational purposes, self-medication or self-harm	None
Baclofen	No	Baclofen is a $GABA_B$ receptor agonist that is prescribed off-label for AUD with mixed findings regarding its efficacy	Pharmacogenetic data are limited to date and focused on GABA receptors
Ondansetron	No	Ondansetron is a 5-HT_3 receptor antagonist that has been prescribed off-label to reduce alcohol consumption in AUD	Initial data suggest that multiple polymorphisms in the serotonin transporter gene (*SLC6A4*), as well as in the 5-HT3 receptor gene may moderate treatment response to ondansetron; however, replication in larger clinical trials is required
Varenicline	No	Varenicline is a partial α4β2 nAChR agonist prescribed for smoking cessation and further prescribed off-label for AUD. Initial data suggest that varenicline might be a promising treatment option for AUD, especially in patients with comorbid nicotine use disorder, however, its efficacy for AUD will have to be demonstrated in rigorous clinical trials	None
Nalmefene	No	Nalmefene is a μ- and δ-opioid receptor antagonist and partial κ-opioid receptor agonist that has been approved for the treatment of AUD in the European Union but not in the United States. While some data suggest that nalmefene may have some efficacy in reducing alcohol consumption, there is not enough high-quality data to establish its value for the treatment of AUD; therefore, carefully designed, well-powered randomized controlled trials are needed to compare nalmefene not only to placebo but also to other approved pharmacological AUD treatments	Limited data are available and no effects were found for opioid related genes
SSRIs and serotonin-related drugs	No	Although SSRIs are widely prescribed for the treatment of depression and anxiety, clinical trials examining the efficacy of SSRIs in treating comorbid AUD, depression and anxiety have shown few promising results, and there are few pharmacogenetic studies of these drugs	While some data suggest some genetic moderation of variation in *5-HTTLPR* on SSRI efficacy in anxious individuals with AUD, at this time these findings have not been replicated and offer little clinical utility

AUD: Alcohol use disorder; GABA: Gamma-aminobutyric acid; nAChR: Nicotinic acetylcholine receptor; SSRI: Selective serotonin reuptake inhibitor.

moderating effects on treatment responses and it would improve treatment outcomes for individuals of different ancestral backgrounds, which would effectively reduce health disparities [193].

To advance pharmacogenetics of AUDs, prospective analyses, not retrospective analyses, are needed. This issue is highly salient in light of the attempt by Oslin *et al.* [55] to show an effect of the *OPRM1* variant Asn40Asp on the treatment response to naltrexone. Previous retrospective pharmacogenetic analyses of this SNP have robustly demonstrated that the Asp40 allele was predictive of reduced relapse rates and lower drinking rates in alcohol-dependent individuals treated with naltrexone compared with the Asn40Asn group [46,49,50,194]. However, Oslin *et al.* failed to find a significant genotype x treatment interaction in their sample, suggesting that 'it is premature to use the Asn40Asp polymorphism as a biomarker to predict the response to naltrexone treatment of alcohol dependence' [55]. Thus, despite previous findings, failure to replicate these effects in larger prospective RCTs indicates that there is currently limited clinical justification for physicians' ordering of genotyping tests to predict naltrexone treatment response, although in the future this will ultimately be the ideal course of action.

Conclusion & future perspective

As the field is evolving, there are several elements that should be included in future studies. First, they should use the standardized set of outcome measures as advised by the FDA to evaluate the efficacy of treatment response. Much of the current controversy in assessing positive or negative findings derives from discrepant drinking outcome measures between studies. Prospective studies therefore need to focus on consistently defining behavior-based outcome measures that will longitudinally reduce the negative consequences of drinking outside of a short-term trial.

Second, trial designs should include a standardized assessment schedule for the assessment of all patients. This standardization will not only aid clinical management of patients but also offer a more consistent method for reporting adverse side effects to medications. An additional problem with current pharmacogenetic studies is their lack of power. Future studies should use adequate sample sizes that are balanced for gender, and appropriately correct for multiple comparisons. With larger, more inclusive samples spanning multiple populations, as discussed above, it will be possible to control for population stratification, a further concern with current studies.

Lastly, there should be standardized minimum gene coverage, and gene x environment interactions should be evaluated to strengthen potential genetic findings. Ultimately, large prospective clinical trials will be the ideal, but they must not demonstrate the same lack of standardization currently seen in the field of pharmacogenetics.

In summary, pharmacogenetics of the treatment of AUDs is a promising field that deserves greater attention in both future research and clinical practice. While it has not yet delivered actionable guidance for implementation in current clinical practice, the goal of precision medicine for AUD with more beneficial treatment responses and minimal side effects for all individuals remains a high priority for the field.

Executive summary

- Alcohol use disorder (AUD) is highly prevalent and associated with high individual and economic costs; however, there are only three US FDA-approved treatments with limited efficacy. Summary information for drugs used in AUD treatment can be found in Table 1.
- Limitations of the pharmacogenetic studies discussed in this review include small-sample sizes, lack of correction for multiple comparisons, a broad phenotype of alcohol use, the use of samples that were not balanced for gender, a primary focus on European ancestry samples and use of retrospective analyses.
- Future prospective pharmacogenetic studies of AUD should use standardized trial designs and outcome measures, inclusive samples spanning multiple populations, adequate sample sizes that are balanced for gender, and they should appropriately correct for multiple comparisons.
- Pharmacogenetics of the treatment of AUDs is a promising field that deserves greater attention in both future research and clinical practice; while it has not yet delivered actionable guidance for implementation in current clinical practice, the goal of precision medicine for AUD with more beneficial treatment responses and minimal side effects for all individuals remains a high priority for the field.

Acknowledgments

The author thanks Christine Muench and Emma O'Connell for helpful suggestions and editing of the manuscript.

Financial & competing interests disclosure

This work was supported by the National Institutes of Health (NIH) intramural funding (ZIA-AA000242 to FW Lohoff); Division of Intramural Clinical and Biological Research of the National Institute on Alcohol Abuse and Alcoholism (NIAAA). The author declares no conflict of interest. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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