HHS Public Access

Author manuscript

Expert Opin Drug Metab Toxicol. Author manuscript; available in PMC 2020 July 01.

Published in final edited form as:

Expert Opin Drug Metab Toxicol. 2019 July ; 15(7): 553–564. doi:10.1080/17425255.2019.1628218.

Pharmacogenetics of alcohol use disorder treatments: an update

Emily E. Hartwell and **Henry R. Kranzler***

Mental Illness Research, Education and Clinical Center, Crescenz VAMC, Philadelphia, PA 19104, USA

Center for Studies of Addiction, Department of Psychiatry, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA 19104, USA

Abstract

Introduction—Alcohol use disorder (AUD) is a highly prevalent; costly economically, socially, and interpersonally; and grossly undertreated disorder. The low rate of utilization of pharmacological treatments with demonstrated efficacy is particularly noteworthy. This is due, in part, to the modest efficacy of the medications approved to treat the disorder. One approach to increasing the utility and safety of these medications is to use precision medicine, which seeks to identify patients for whom specific medications are likely to have the most robust therapeutic effects and the fewest adverse effects.

Areas Covered—Here we review the current literature on the pharmacogenetics of AUD treatment. We cover both laboratory studies and clinical trials that have provided valuable insights into the mechanisms and value of precision-based care for AUD. We discuss studies of genetic moderators for personalizing pharmacotherapy with medications approved by regulatory agencies in the United States and Europe and those that are used off-label to treat AUD.

Expert Opinion—Pharmacotherapy can be a useful component of AUD treatment. Currently, the evidence regarding genetic predictors of medication efficacy is very limited. Thus, precision medicine is not yet ready for widespread clinical implementation. Further research is needed to identify candidate genetic variants that moderate the response to both established and novel medications in development for this goal to be achieved. The growing availability of large-scale, longitudinal datasets that enable the synthesis of genetic and electronic health record data could provide important opportunities to develop this area of research.

***Corresponding author:** Henry R Kranzler, University of Pennsylvania, Center for Studies of Addiction, 3535 Market Street, Suite 500, Philadelphia, PA 19104; Telephone: 215-823-5800; kranzler@pennmedicine.upenn.edu.

Declaration of Interest

H Kranzler is a member of the American Society of Clinical Psychopharmacology's Alcohol Clinical Trials Initiative, which, in the last three years, was supported by AbbVie, Alkermes, Amygdala Neurosciences, Arbor Pharmaceuticals, Ethypharm, Indivior, Lilly, Lundbeck, Otsuka, and Pfizer. H Kranzler is named as an inventor on PCT patent application #15/878,640 entitled: "Genotype-guided dosing of opioid agonists," filed January 24, 2018. The authors have 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.

Reviewer Disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Keywords

Alcohol use disorder; pharmacogenetics; precision medicine; pharmacotherapy; genetic moderators

1. Introduction

Alcohol use disorder (AUD) is highly prevalent, with estimates ranging from 5.6% [1] to nearly 14% [2] of U.S. adults meeting criteria for the disorder during the preceding year and approximately 6% of the population endorsing heavy drinking in the past month [3]. The fifth and latest edition of the Diagnostic and Statistical Manual (DSM), published in 2013 by the American Psychiatric Association, changed the previously used distinct diagnostic categories of alcohol dependence and abuse into a unidimensional AUD diagnosis with a severity specifier. The first and second editions of the DSM, first published in 1952, used the diagnostic term “alcoholism,” however, as this term is imprecise and ambiguous, the term AUD is preferred. To be diagnosed with AUD, an individual must report problematic alcohol use leading to significant distress or impairment, endorsing at least two of the 11 diagnostic criteria [4], which are grouped into impaired control, social impairment, risky use, and pharmacological categories. A severity specifier based on the number of criteria endorsed divides AUD into “mild” (2–3 criteria), “moderate” (4–5 criteria), and “severe” (6 or more criteria).

AUD, which usually has its onset before age 40 [2], is commonly associated with high rates of psychological and physical comorbidities, social and familial disruption, and decreased work productivity. Although the central feature of AUD is impaired control over drinking and it is characterized by episodic heavy drinking and/or the daily consumption of large amounts of alcohol, it is highly heterogeneous in its presentation and course.

The estimated heritability of AUD ranges from 40–70% [5, 6, 7], which also reflects a substantial environmental contribution to risk of the disorder [8]. Various endophenotypes, including the subjective response to alcohol and neurobiological vulnerabilities, which are partially heritable, can be strong predictors of who will develop an AUD [9]. Understanding the factors contributing to the development and the pathophysiology of AUD can inform treatments for the disorder [10].

Alcohol is a unique substance of abuse because it does not have a specific receptor on which it acts, exerting its central nervous system effects through interactions with a host of neurotransmitter systems. Research has examined the impact of alcohol on opioidergic, dopaminergic, GABAergic, glutamatergic, and serotonergic neurotransmission and the genes the encode the proteins in these systems [10, 11]. GABAergic and glutamatergic systems are inhibitory and excitatory, respectively, and dysregulation of these neurotransmitters leads to impaired learning, tolerance, and seizures [11]. The dopaminergic system is involved in motivation, reinforcement, motor control, and hormonal response. The ingestion of alcohol increases dopaminergic transmission [11]. Alcohol administration also increases endogenous opioid activity, which regulates mood, pain, emotions, and reinforcement [11]. Finally, serotonin is associated with mood, thought, and sleep and eating behaviors, which are

modified by its release in response to small amounts of alcohol [11]. The actions of these various neurotransmitter systems are intertwined, further complicating our understanding of the impact of alcohol on the brain and its pharmacogenetic effects. For example, the release of serotonin stimulated by alcohol consumption may in turn increase dopamine release and associated emotional behaviors [12].

Despite AUD's high prevalence and cost to individuals, families, and society, less than 20 percent of individuals with the disorder seek and receive alcohol treatment [2] and only a small fraction of these individuals are prescribed a medication with demonstrated efficacy in reducing heavy drinking or promoting abstinence [13]. Reasons for this low rate of seeking treatment include its high cost, limited availability, and the inadequate knowledge or skill of providers [14, 15]. As with the course and presentation of AUD, variation in the efficacy of AUD treatment can be influenced by genetic variation. Thus, recently, there has been considerable interest in personalized, stratified, or precision medicine, which is characterized by the tailoring of treatments to individuals based on key characteristics, such as genetics, environment, and lifestyle, to maximize the efficiency and benefit to patients. Of particular interest here are efforts to tailor pharmacotherapy to individuals' specific genetic profiles in order to enhance treatment adherence (by reducing adverse effects) and improve outcomes (by increasing the therapeutic response).

Currently, there are three medications approved by the U.S. Food and Drug Administration (FDA) for the treatment of AUD: disulfiram, acamprosate, and naltrexone (both oral and injectable formulations). Disulfiram, which was approved in 1949, acts by inhibiting the metabolism of acetaldehyde, a toxic intermediary metabolite of ethanol, causing an unpleasant physiological reaction [16]. Naltrexone, approved by the FDA in 1994, is a μ-, κ-, and δ- opioid receptor antagonist that modulates the dopamine-mediated rewarding effects of alcohol and reduces its consumption [10, 16]. In 2006, a long-acting, injectable formulation of naltrexone was approved for treating AUD. Although the exact mechanism of acamprosate's effects is unclear, it appears to modulate glutamatergic neurotransmission and was FDA approved in 2004 [17].

Nalmefene and baclofen are approved in the European Union and France, respectively, but not in the United States. Nalmefene, a μ- and δ-opioid receptor antagonist and a κ-opioid receptor partial agonist, was efficacious in reducing binge drinking and overall alcohol consumption in three European trials [18, 19, 20]. Baclofen is a $GABA_B$ receptor agonist that has shown efficacy in maintaining abstinence [16, 21]. At present, there are also over 30 compounds in Phase I and II clinical trials in the United States, 75% of which are FDA approved for other indications. The preclinical and clinical safety evaluations conducted in support of the approval of these medications will reduce the time and expense of developing them for use in treating AUD [22].

Strategies to enhance treatment response to the various medications under investigation include personalized treatment through the application of pharmacogenetics, which focuses on the genetic moderation of the pharmacokinetic and pharmacodynamic effects of a medication. Pharmacodynamic effects refer to the drug's effect on the body, which include receptor-mediated effects that produce both therapeutic and adverse effects. Pharmacokinetic

effects refer to the impact of the body on the drug and include effects on its absorption, distribution, metabolism, and excretion. Here, we review pharmacogenetic studies (published through November 2018), including both randomized controlled trials (RCTs) and human laboratory studies relevant to treating AUD. The review covers both FDA-approved medications and those in development.

2. Pharmacogenetics of AUD Medications

2.1 FDA Approved Medications

2.1.1 Naltrexone—Of the three FDA-approved medications, the pharmacogenetics of naltrexone has been studied most extensively. An opioid receptor antagonist, naltrexone exerts a small, but statistically reliable, effect in treating AUD [23, 24], principally by reducing heavy drinking and craving [25]. However, not all studies have shown naltrexone to be efficacious in treating AUD (e.g., [26]). In an effort to personalize AUD treatment and enhance naltrexone's efficacy, pharmacogenetic studies of the medication (summarized in Table 1) have examined the moderating effects of the Asn40Asp single nucleotide polymorphism (SNP) in exon 1 of the μ-opioid receptor gene (*OPRM1*). *OPRM1* encodes a protein in the endogenous opioid system that is thought to be involved in pleasure and reward pathways. It has been hypothesized that variation in *OPRM1* contributes to the risk of substance use disorders and to food preferences, pain perception, and physiological stress reactivity [27, 28]. The first report suggesting such an effect came from a secondary analysis of 141 participants from three 12-week, placebo-controlled RCTs [29]. The analysis showed that European-American carriers of the minor Asp40-allele were associated with a higher rate of relapse to heavy drinking when treated with placebo than naltrexone [odds ratio (OR)=3.52], with no difference in relapse rate in individuals homozygous for the Asn40 allele [29]. Asp40 carriers treated with naltrexone also took longer to relapse to heavy drinking than Asn40 homozygotes treated with naltrexone (OR=2.79). However, it should be noted that, in this analysis, the interaction of gene by medication was not significant for any treatment outcome measure. Conversely, such an interaction was seen in the COMBINE study [30], where a secondary analysis was conducted in 604 Caucasian participants who provided genetic samples [31]. The analysis demonstrated a strong moderating effect of the *OPRM1* genotype, such that Asp40-allele carriers treated with naltrexone were significantly more likely to show a good clinical outcome than either Asn40-allele homozygotes or either of the genotype groups treated with placebo. Asp40-allele carriers treated with naltrexone also reported a significantly lower percentage of heavy drinking days and a significantly higher percentage of abstinent days than either Asn40 homozygotes or the two placebo groups.

Despite these promising initial findings, subsequent RCTs that examined the moderating effect of the Asn40Asp SNP on the response to naltrexone have yielded conflicting findings. One example of this involves a secondary analysis of data from the Department of Veterans Affairs Cooperative Study 425, which examined the efficacy of 12 weeks or one year of naltrexone treatment in male veterans with alcohol dependence [26]. In a subset of study participants (N = 220 or 35.1% of the total sample), seven polymorphisms in *OPRM1*,

OPRD1, and *OPRK1* were examined as potential moderators of naltrexone response [32]. None of the SNPs were found to moderate the medication response.

Although clinical trials typically seek to limit participant heterogeneity by excluding individuals with co-occurring psychiatric disorders, two trials tested pharmacogenetic moderation of naltrexone's effects in dually diagnosed individuals. Arias et al. [33] recruited 107 European-American, alcohol-dependent, male veterans with a comorbid Axis I disorder to participate in a 12-week trial in which they were randomized to receive treatment with naltrexone, placebo, disulfiram and naltrexone, or disulfiram and placebo. Study participants were genotyped for the Asn40Asp SNP in *OPRM1* and rs1611115 in the dopamine β-hydroxylase (*DBH*) gene, which encodes a key enzyme in the conversion of dopamine to norepinephrine. Inhibition of DBH is associated with psychosis and major depression [34]. Despite there being no effects of the *OPRM1* SNP, the study showed that the *DBH* variant moderated the response to naltrexone, such that T-allele carriers who received naltrexone were less likely to report heavy drinking. In a second study, 108 alcohol-dependent patients with major depression were treated with naltrexone and randomly assigned to receive citalopram or placebo [35]. The results showed no moderating effects of the Asn40Asp SNP on any of the alcohol consumption outcome measures tested, including percent days abstinent (Cohen's d=0.06), drinks per drinking day (d=0.00), and heavy drinking days (d=0.04).

Because of the bias inherent in secondary analyses, two RCTs prospectively genotyped individuals for the Asn40Asp SNP, stratifying the randomization to naltrexone or placebo on genotype. Both trials oversampled individuals with an Asp40 allele. The first study, a 12-week trial in 221 alcohol-dependent subjects from five sites across Pennsylvania, showed no evidence of a gene-by-medication interaction on heavy drinking, the primary outcome (OR=1.10 for Asp40 carriers treated with naltrexone versus placebo), abstinence, or any other alcohol-related outcome, including craving [36]. The second study, a 16-week trial in 151 alcohol-dependent individuals, showed an overall reduction in heavy drinking in the naltrexone group, with no evidence of moderation by *OPRM1* genotype [37]. The authors of this report noted that, although the genotype by medication interaction was not significant, the effect size (Cohen's d) for the difference between naltrexone and placebo was 1.1 for Asp40-allele carriers, but only 0.19 for Asn40-allele homozygotes. In addition, there was a significant interaction of genotype, medication, and time, with Asp40-allele carriers treated with naltrexone showing an increase in the rate of heavy drinking once the medication was stopped, whereas heavy drinking in the other groups remained stable [37]. In an open-label study, 100 Australian alcohol-dependent individuals treated with naltrexone for 12 weeks significantly decreased both self-reported and objective indicators of alcohol use and craving from baseline levels. However, there was no evidence of a significant association between the *OPRM1* Asn40Asp genotype and any of the outcome measures [38].

Another factor that complicates the interpretation of these findings is the wide variation in the prevalence of the *OPRM1* Asp40 allele in different population groups. Individuals of East Asian descent have a much higher prevalence of the allele than other populations (i.e., up to 50% of Japanese compared with approximately 20% in European Americans and 3% in African Americans), thus the potential moderating effects of the SNP could differ

substantially by population [39]. In a laboratory study of 29 healthy individuals (59% Asian ancestry), naloxone was administered intravenously to investigate *OPRM1* mediation of HPA-axis activation [40]. Results showed that European-American Asp40-allele carriers had a greater cortisol response than Asn40 homozygotes, however, the effect was not observed in participants of Asian descent. In a 12-week open-label trial of 63 Koreans with alcohol dependence, 32 individuals who were medication adherent were genotyped [41]. Half of the sample was Asp40-allele carriers, who were free of relapse for a significantly longer period of time than the Asn40-allele homozygotes (hazard ratio=13.6, p=0.01). Although not statistically significant, Asn40 homozygotes had a 10.6 times greater relapse risk than Asp40-allele carriers. This study was limited by the absence of a control group and the bias introduced by including only medication-adherent patients. A subsequent laboratory study examined whether such findings would obtain in Asian Americans (N = 35; [42]). Using a double-blind, counterbalanced within-subjects design, participants underwent intravenous alcohol administration after receiving treatment with naltrexone or placebo for four days. The procedure was then repeated with participants being switched to the other medication group. Asp40-allele carriers reported less craving for alcohol when treated with naltrexone than placebo during the alcohol administration period. A larger study of the pharmacogenetic effect of subjective response to and self-administration of alcohol in Asian Americans used a similar double-blind design [43], with 77 East Asian participants undergoing two counterbalanced sessions in which they were administered naltrexone or placebo for five days followed by an experimental session in which they received an intravenous priming dose of alcohol followed by a period of alcohol self-administration. Contrary to this group's prior findings, no pharmacogenetic interaction with medication was observed for either the alcohol-induced subjective response or alcohol self-administration in the laboratory session. In sum, differential effects of *OPRM1* based on population have been observed [40, 44], however, those findings are inconsistent, making interpretation difficult.

Laboratory studies, in addition to RCTs, have also been used to evaluate moderation by the Asn40Asp SNP of naltrexone-induced reductions in alcohol consumption. Ray and Hutchison [45] conducted a double-blind, within-subjects alcohol challenge study in which 40 participants genotyped for the SNP were administered placebo or naltrexone and assessed at four ascending breath alcohol concentrations (BrACs): 0.00, 0.02, 0.04, and 0.06 mg/dL. They found that Asp40-allele carriers reported greater blunting of self-reported alcohol-induced high following treatment with naltrexone than placebo, particularly at higher BrACs. A subsequent analysis of the same laboratory study [46] included SNPs in *OPRK1* and *OPRD1*, which encode the kappa-opioid and delta-opioid receptors, respectively, receptors that are also blocked by naltrexone. There is mixed evidenced that variation in these genes is associated with alcohol, opioid use, and cocaine use disorders [47, 48, 49]. The study yielded two gene-by-medication interactions. Following naltrexone treatment, *OPRK1* rs997917*T-allele homozygotes reported less alcohol-induced sedation than C-allele carriers and *OPRD1* rs4654327*A-allele carriers reported lower levels of alcohol stimulation and craving than G-allele homozygotes. These findings contrast with the earlier null findings for these variation in Gelernter et al.'s [32] analysis of data from the VA Cooperative Study of naltrexone. Setiawan et al. [50] studied 40 "social drinkers," defined as drinking at least five drinks per week and reporting no alcohol-related problems. Study

participants completed an alcohol self-administration task after six days of naltrexone treatment. They found that alcohol-induced euphoria was significantly blunted among Asp40-allele carriers treated with naltrexone, findings similar to those of Ray and Hutchison [51]. In contrast, a laboratory study of 93 participants who completed a cue-reactivity paradigm [52] yielded a gene-by-medication effect that was opposite in direction to these findings. In this study, following 10 days of naltrexone treatment, Asp40-allele carriers reported a heightened urge for alcohol [effect size (η^2_p)=0.73], with no effect observed in Asn40-allele homozygotes [52]. The study also examined the effects of a variable number of tandem repeats polymorphism in *DRD4*, which encodes the dopamine receptor. *DRD4* has been implicated as contributing to substance use, attention deficit hyperactivity disorder, and various personality traits [53, 54, 55, 56]. However, it showed no moderating effect (η^2_p<0.06) in this study. It is important to note that these laboratory studies were generally conducted in small samples and did not correct for multiple comparisons. Further, the study participants differed among the studies, making it difficult to draw conclusions on the moderating effect of the Asn40Asp SNP on the response to naltrexone.

One approach to addressing the small sample size of pharmacogenetic studies, a limitation that contributes to the risk of a Type 2 error, is to aggregate the effects from multiple studies using meta-analysis. Chamorro and colleagues [57] meta-analyzed six naltrexone treatment studies (N = 764) that evaluated the moderating effect of the Asn40Asp SNP on the likelihood of relapse or abstinence in patients with alcohol dependence. They found that naltrexone treatment in Asp40-allele carriers was associated with lower rates of relapse to heavy drinking than Asn40 homozygotes (OR: 2.02, CI: 1.26–3.22), though there was no evidence of genetic moderation of naltrexone's effects on the rate of abstinence. A subsequent meta-analysis included eight studies (N = 1,365) in which drinking level was assessed [58]. This analysis showed no significant difference between Asp40-allele carriers and Asn40 homozygotes on the likelihood of a return to heavy drinking during naltrexone treatment.

In summary, evidence of a pharmacogenetic effect of variation in *OPRM1* on the response to naltrexone in clinical trials and laboratory studies have yielded mixed results, though the most experimentally rigorous studies have failed to show consistent evidence of an effect. Though beyond the scope of this review, pharmacogenetic studies of naltrexone using functional magnetic resonance imaging have also shown inconsistent findings regarding moderation by the Asn40Asp SNP [37, 59, 60, 61]. This lack of consistent findings is likely due to multiple factors, which are discussed in the Expert Opinion section.

2.1.2 Disulfiram—Disulfiram, the first FDA-approved medication for treating AUD, exerts its therapeutic effects by blocking the metabolism of acetaldehyde, a toxic intermediary metabolite of alcohol. A rapid rise in acetaldehyde occurs when a disulfiram-treated individual consumes alcohol, resulting in an aversive reaction (e.g., flushing, nausea, tachycardia, sweating), the prospect of which is thought to discourage drinking. Although, as described above, *DBH* rs1611115*T-allele carriers reported fewer drinks per drinking day than rs1611115*C-allele homozygotes [33], there was no moderating effect of *OPRM1* on outcomes following disulfiram treatment. A study in 109 Japanese men diagnosed with alcohol dependence who were treated with either disulfiram or placebo for 26 weeks

examined the moderating effect of the null *ALDH2* allele, which is present in up to half of individuals of East Asian ancestry [62, 63]. Of the 15 participants with this genotype, those treated with disulfiram were more likely to be abstinent at the end of treatment than those who received placebo. To date, there have been no reported efforts to replicate the findings of either of these studies.

2.1.3 Acamprosate—Although the mechanism of action of acamprosate in treating AUD remains to be fully elucidated, and its effects on reducing the risk of relapse to drinking in abstinent patients are modest, the medication is widely available for treating AUD [64]. It was approved in the United States in 2004 based on findings from three European trials that showed it to be efficacious in preventing abstinent patients from relapsing to drinking. It was hypothesized to act via its glutamatergic effects [10]. Ooteman et al. [65] compared the effects of 21 days of treatment with acamprosate or naltrexone on cue-induced craving and examined the moderating effect of SNPs in *OPRM1*, *DRD1*, *DRD2*, *GRIN2B*, *GABRA6*, *GABRB2*, and *GABRG2*. Although they found that variants in *DRD2*, *GABRA6*, and *GABRB2* moderated the response to acamprosate, the authors used an alpha level of 0.10 and failed to correct for multiple comparisons. Thus, the results should be seen as preliminary and replication in larger samples is necessary. Karpyak and colleagues [66] examined 548 candidate SNPs in a discovery sample of 225 European-American alcohol-dependent patients evaluated after three months of treatment with acamprosate. They identified two SNPs in *GRIN2B* (rs2300272 and rs2058878), which encodes a subunit of the NMDA receptor, that has been linked to neurodevelopmental disorders such as intellectual disabilities. They found two nominally significant moderators of abstinence outcomes. Specifically, the minor (G) allele of rs2300272 was associated with a shorter abstinence duration and the minor A allele of rs2058878 was associated with a longer period of abstinence. However, when corrected for multiple comparisons only rs2058878 was significantly associated with the length of abstinence during acamprosate treatment. Although this study did not have a control group, a replication analysis in 110 males from the PREDICT study showed a non-significant trend for an association of abstinence length with rs2058878 (hazard ration=0.72, p=0.07). A prior pharmacogenetic analysis from the three-month PREDICT study implicated rs13273672, a SNP in *GATA4*, as a moderator of the effects of acamprosate on relapse risk, with G-allele homozygotes relapsing to heavy drinking sooner than the other genotype groups [67]. To date, there have been no published efforts to replicate this finding, though a study of *GATA4* variants with alcohol dependence risk showed an association at the gene level, rather than specifically with rs13273672 [68].

2.2 Medications That Are Not Approved in the United States for Treating AUD

2.2.1 Nalmefene—In 2013, nalmefene, a mu- and delta-opioid receptor antagonist, and a kappa-opioid receptor partial agonist, was approved in the European Union for treating AUD, though the literature is not wholly consistent regarding its efficacy [69, 70]. An early study in Finland randomly assigned 403 alcohol-dependent individuals to receive 10–40 mg of nalmefene or placebo on an as-needed basis (i.e., participants were instructed to take the medication when they believed that drinking was imminent) for 28 weeks [71]. The nalmefene-treated group reported fewer heavy drinking days and showed greater

improvement on alcohol-related biomarkers than the placebo group. A secondary analysis of data from 272 participants in this study examined the moderating effect of two SNPs in *OPRM1*, two SNPs in *OPRD1* (which encodes the delta-opioid receptor), and one SNP in *OPRK1* (which encodes the kappa-opioid receptor) on the response to nalmefene. The study found no main or moderating effects of these genotypes on drinking outcomes [72].

2.2.2 Topiramate—Pharmacogenetic effects of topiramate, an anticonvulsant that is efficacious in the treatment of AUD [73], have also been investigated. Topiramate has multiple pharmacologic effects, including the antagonism of glutamate activity at AMPA and kainate receptors [74, 75] and has been shown to be effective at reducing alcohol consumption, increasing abstinence, and lessening craving [76, 77]. Topiramate's effects on glutamate receptors are most potent and selective for those containing the GluK1 and GluK2 subunits (encoded by *GRIK1* and *GRIK2*, respectively)[78, 79], which have been linked to schizophrenia, Huntington's disease, and obsessive-comuplsive disorder, although the findings are inconsistent [80, 81, 82]. To identify a suitable candidate genetic biomarker, Kranzler et al. [83] used an association study in alcohol-dependent cases and controls to examine variation in *GRIK1* as a potential moderator of the response to topiramate in treating AUD. They found that, of seven SNPs examined, three were nominally associated with alcohol dependence. Using empirical p-value estimation, only one, rs2832407 (C allele), was significantly associated with the disorder.

Ray and colleagues [84] examined whether the three *GRIK1* SNPs identified previously as nominally significant [83] moderated the severity of adverse events in 51 heavy drinkers treated with topiramate or placebo for five weeks. They found that rs2832407*C-allele homozygotes reported a lower severity of adverse events than A-allele carriers. Subsequently, Kranzler and colleagues [85] tested the hypothesis that rs2832407 moderates the response to topiramate in a 12-week, placebo-controlled RCT in heavy drinkers. Analysis of the 122 European-American participants revealed that rs2832407*C-allele homozygotes treated with topiramate reported a significantly greater and more rapid reduction in heavy drinking days and a greater and more rapid increase in abstinent days than both placebo-treated patients and topiramate-treated patients who were heterozygotes or rs2832407*A-allele homozygotes. These investigators did not replicate the previously observed finding that the SNP moderated the adverse effects of topiramate. In a secondary analysis of these data that combined the number needed to treat (NNT) to prevent any heavy drinking in the last month of treatment with the number needed to harm (NNH), i.e., that resulted in a moderate or severe adverse event at any time during the 12-week trial. Among rs2832407*C-allele homozygotes, the NNT for topiramate when adjusted for the NNH was <3, while for A-allele carriers it was >300 [86]. If replicated, these findings would argue strongly for the use of topiramate only in rs2832407*C-allele homozygotes. A post-treatment follow-up of these subjects three and six months after the study medication was discontinued showed that heavy drinking remained low among C-allele homozygotes treated with topiramate [87].

These results, while compelling, require independent replication. Ongoing clinical trials in both the United States (https://clinicaltrials.gov/ct2/show/NCT02371889) and Australia [88]

are prospectively randomizing individuals with AUD based on rs2832407 genotype in an effort to replicate the SNP's moderating effect.

2.2.3 Sertraline—Selective serotonin reuptake inhibitors (SSRIs), which increase serotonin levels in the synapse, are FDA approved for treating anxiety disorders and major depression. In preclinical models, serotonin levels are inversely related to alcohol consumption and in long-term alcohol users there is evidence of serotonin system dysregulation [89, 90]. SSRIs, including sertraline, which facilitates 5-HT transmission while inhibiting dopamine, thus potentially reducing the reward associated with alcohol administration [91], have been tested as treatments for AUD to variable effect [92, 93, 94]. In heterogeneous alcohol dependent populations, these medications have yielded mixed evidence of efficacy, leading to efforts to subtype patient samples to identify both phenotypic and genetic moderators of treatment response [95].

In a study of sertraline for treating AUD [89], 134 participants who were characterized as having either early-onset (i.e., by age 25) or late-onset (i.e., after age 25) alcohol dependence and were genotyped for the tri-allelic serotonin-transporter-linked polymorphic region (5-HTTLPR) polymorphism, which consists of L' and S' alleles. This insertion-deletion polymorphism in *SLC6A4* encodes the serotonin transporter, which plays a key role in serotonin signaling in the central nervous system. 5-HTTLPR has been linked to alcohol craving [96] and a host of psychiatric phenotypes, including mood, anxiety, suicidality, and the response to trauma [97, 98, 99, 100] Daily alcohol consumption was assessed during the 12-week pharmacotherapy trial and participants were randomly assigned to receive treatment with placebo or up to 200 mg/day of sertraline. The study showed that the effect of sertraline was moderated by age of onset and genotype group, such that among L' homozygotes, those with late-onset alcohol dependence reported fewer drinking and heavy drinking days when treated with sertraline than placebo. In contrast, L' homozygotes with early-onset AUD who were treated with placebo reported fewer drinking days and heavy drinking days than those receiving sertraline. There were no effects in S'-allele carriers. As noted by the authors, there was high rate of attrition in this study, particularly amongst early-onset L' homozygotes, and the results require replication in larger samples.

Kenna et al. [91] examined the pharmacogenetics of two serotonergic medications in a randomized, crossover laboratory study of 77 non-treatment-seeking individuals with alcohol dependence. Participants were randomly assigned to receive three weeks of treatment with sertraline 200 mg/day or ondansetron 0.5 mg/day, placebo for three weeks, and followed by the alternative medication (sertraline or ondansetron) for three weeks. Each three-week treatment period was followed by a laboratory assessment. They examined the moderating effect of the bi-allelic 5-HTTLPR polymorphism (which yields SS, SL, and LL genotypes) and found that women with an S allele drank fewer drinks per drinking day than L-allele homozygotes when treated for three weeks with sertraline. The results for men were not significant. There was also a three-way interaction of 5-HTTLPR and *DRD4* genotypes and medication, such that S-allele carriers with the *DRD4*<7-repeat allele treated with sertraline drank less during the laboratory session and in the naturalistic period for the duration of the trial. These complex preliminary findings in both a clinical trial and a

laboratory study require replication before they can be used to inform the pharmacogenetics of AUD treatment.

2.2.4 Ondansetron—Ondansetron, a 5-HT_3 receptor antagonist that is approved as an antiemetic [101, 102], has also been evaluated for the treatment of AUD. The medication has been shown to reduce craving, lengthen periods of abstinence, and reduce heavy drinking in participants with AUD in whom it may reduce the rewarding effects of alcohol [64, 101]. Johnson et al. [103] randomly assigned 283 alcohol-dependent individuals to receive 11 weeks of treatment with ondansetron 4 μg/kg twice daily or placebo, together with cognitive behavioral therapy. The randomization was stratified using the bi-allelic 5-HTTLPR polymorphism and participants were also genotyped for a SNP (rs1042173) in the 3' untranslated portion of the serotonin transporter gene, *SLC6A4*. Results indicated that among L-allele homozygotes, those treated with ondansetron reported fewer heavy drinking days, fewer drinks/drinking day, and higher abstinence rates than those treated with placebo. There was no effect of ondansetron among S-allele carriers. Finally, there was a gene-gene interaction, such that 5-HTTLPR*L-allele homozygotes who were also rs1042173*T-allele homozygotes reported consuming the fewest drinks per drinking day and having the highest percent days abstinent of the four genotype-by-medication groups. A secondary analysis of these data was conducted that included 19 SNPs in *HTR3A* and *HTR3B*, the genes encoding the 5-HT3 receptor, a key binding site for ondansetron [104]. It identified an additional three genotypes that moderated the response to ondansetron. Using these SNPs and the two previously identified polymorphisms in *SLC6A4*, it was possible to categorize 34% of European-Americans as having at least one of the five ondansetron-responsive genotypes. Further, individuals possessing any combination of three identified *HTR3A* or *HTR3B* genotypes had a five-fold likelihood of having no heavy drinking days when treated with ondansetron compared to placebo. The authors referred to this subgroup as "super responders" [104].

Kenna et al. [91], using the crossover study design described above, examined the pharmacogenetics of the response to ondansetron [105]. They found that ondansetron modestly reduced naturalistic drinking in 5-HTTLPR L-allele homozygotes, but the effect was not seen in the laboratory self-administration part of the trial.

Overall, the initial findings of beneficial effects of ondansetron on drinking in the naturalistic setting are promising, as the medication exerted these effects at a very low dosage, at which it is well tolerated. An ongoing trial (https://clinicaltrials.gov/ct2/show/record/NCT02354703) seeks to replicate and expand upon the findings reported by Johnson et al. [104].

2.2.5 Baclofen—Baclofen, a $GABA_B$ receptor agonist, was recently approved for AUD treatment in France, though the findings from RCTs are not consistent in supporting its efficacy for that indication [16]. Some of the heterogeneity in the response to baclofen may be due to the presence of psychiatric comorbidity in some study populations [21]. In view of the mixed findings, further research on its use is required, leading to a recent consensus statement recommending that it be considered a second-line pharmacotherapy for AUD [106]. In the only published pharmacogenetic study of baclofen, Morley and colleagues

[107] analyzed data from a subset of alcohol-dependent participants who were randomly assigned to treatment with baclofen (30 or 75 mg/day) or placebo. In the secondary analysis, they examined the moderating effect of rs29220 in *GABBR1*, a subunit of the $GABA_B$ receptor gene in 72 subjects. $GABA_B$ impacts reward signaling and has been implicated in various psychiatric and neurological disorders including schizophrenia, substance use disorders, and epilepsy [108, 109, 110, 111]. They found that rs29220*C-allele homozygotes treated with baclofen reported a longer time to relapse and greater proportion of abstinent days than those treated with placebo or baclofen-treated participants with one or two rs29220*G alleles. They also explored the moderating effects of rs29230 of *GABBR1* and rs7865648 of *GABBR2* (which encodes a second $GABA_B$ receptor subunit), but found no significant effects of these SNPs. They concluded that variation in the rs29220 allele frequency by population may help to explain the lack of efficacy of baclofen in some studies. Further study of this potentially useful medication, along with genetic predictors of treatment response, appears warranted.

3. Expert Opinion

In sum, the literature on the pharmacogenetics of AUD treatment is not yet adequate to inform clinical practice. There remains a paucity of pharmacogenetic trials in the field, which is not surprising in that overall the literature supporting medication efficacy in AUD is limited, as is our understanding of the mechanism of action of these medications [24, 112]. Although initial studies have yielded evidence of a number of promising genetic moderators of pharmacotherapeutic response, many of these studies have been conducted in small samples, potentially yielding false positive or false negative findings. In addition, some studies failed to correct for multiple comparisons or to conduct intent-to-treat analyses and were inconsistent in their selection of participants' level of alcohol consumption, severity of AUD, and demographic features. These methodological shortcomings limit the interpretation of these studies' findings and make comparison across studies difficult. Prospective studies, the optimal approach to validating a pharmacogenetic hypothesis, when they have been attempted, have yielded null or clinically insignificant effects. Until there exists a more extensive set of studies in which individuals with AUD are prospectively randomized to active and placebo conditions using an empirically-based pharmacogenetic moderator, the selection of medications to treat the disorder will remain largely a matter of trial and error.

Because AUD is a heterogeneous disorder, variability in sample characteristics complicate efforts to identify a moderating effect of genetic variation. Treatment-seeking status, for example, has a potentially important effect on outcomes in alcohol treatment research [113, 114], as heavy drinkers may be drawn from a different population than individuals with an established AUD diagnosis. Oliver and McClernon [115] argued that attention should also be paid to the timing of the intervention and the temporal course of the disease being treated rather than considering the treatment or its genetic moderation as static features. Psychosocial interventions, including medication management [116], are commonly used in conjunction with medications. Thus, they are an important factor in determining treatment outcomes, as the combination of medication and psychosocial therapy potentially results in better outcomes than either alone [117].

The studies discussed in this review used a wide range of outcome measures, including good clinical outcome [31], subjective response [43], and self-reported alcohol use [36, 85], which limits comparisons across trials and the interpretation of divergent findings. This highlights the need for cost-effective, reliable, and valid biomarkers for alcohol use [118, 119], which could standardize outcome assessments and increase their validity. The size of a standard alcoholic beverage differs across countries, making cross-national comparisons between studies more difficult. The reliance on self-reported alcohol use as an outcome measure, in addition to likely providing an underestimate of drinking, fails to account for improvements in psychosocial functioning and quality of life, important goals of treatment, which have been shown to improve with even small reductions in alcohol consumption [120]. Endophenotypes, such as the subjective response to alcohol [121] or sub-phenotypes, such as the type of reinforcement drinking that characterizes participants [122], could be tested as treatment targets or incorporated in models of treatment outcome, given their greater proximity to underlying genetic variation and the neurobiological changes that result from alcohol use. A heretofore neglected consideration in the design of pharmacogenetic RCTs is the extent to which the placebo effect is heritable [123, 124]. Publication bias, including the "file drawer" effect in which negative or null studies are not published [10], could also contribute to difficulties in interpreting the pharmacogenetic literature.

Although several of the SNPs studied as genetic moderators of AUD treatment have strong biological plausibility, we do not yet fully understand the function of many genes or the impact of variation in them, which limits opportunities for discovery and the interpretation of pharmacogenetic findings [125]. It is possible that, due to the polygenic nature of AUD, individual polymorphisms, such as the Asn40Asp SNP in *OPRM1*, exert small effects on the development and maintenance of AUD without having a clinically meaningful moderating effect on the response to pharmacotherapy [125].

Numerous genome-wide association studies have identified variants in the aldehyde and alcohol dehydrogenase enzyme genes that can substantially affect alcohol metabolism [126, 127, 128]. Whereas most of the medications reviewed here (e.g., naltrexone, ondansetron, and sertraline) are largely metabolized in the liver, the effects of genetic variation on the pharmacokinetics of these medications is also of potential importance in advancing the precision treatment of AUD [129].

Several practical limitations exist in conducting research on the pharmacogenetics of AUD treatment. Other specialty areas, such as oncology, are much further along in the development of this and other aspects of precision medicine [130]. Contributing to this disparity is the disproportionately greater funding provided to the National Cancer Institute, for example, than the National Institute on Alcohol Abuse and Alcoholism, despite the high prevalence and social impact of AUD and its causal relation to a variety of cancers [130]. As a result, there are well understood pharmacogenetic approaches to tumor treatment that are now widely used clinically. For example, tumors characterized by mutations in *EGFR* that cause overexpression of the EGFR protein are linked to a poorer prognosis in several types of cancer. Treating individuals whose tumors carry the mutation with protein kinase-inhibiting drugs has been shown to increase response rates from 10% to 75% [130, 131].

Unfortunately, addiction medicine has no such dramatic examples of pharmacogenetic effects.

Because AUD is associated with a variety of physical and mental health disorders, progress in understanding the etiology and advancing the treatment of AUD can yield benefits in other areas of medicine. Once valid moderators of pharmacotherapy for AUD are identified and validated, disseminating and implementing them in practice will require a concerted effort to educate providers, many of whom still do not routinely prescribe medications with demonstrated efficacy in treating the disorder [16, 132]. A contributor to the low rate of medication use to treat AUD [13, 14] may be resistance from patients. Thus, patients will need to be educated in the utility and clinical relevance of both pharmacotherapy and genetics, before these can assume a central role in the treatment of AUD. Further, the implementation of pharmacogenetics in clinical settings will require staff training, logistical support (e.g., updating electronic health record systems and laboratories), enhanced cybersecurity, and changes in policies regarding insurance coverage.

The revolution in genetics that was ushered in by the sequencing of the human genome will benefit precision medicine in all areas of medicine, including the pharmacogenetics of AUD treatment. Recent strides have been made in recruiting large samples for genetics studies, which have yielded databases that are useful for the discovery of variants contributing to the risk of disorders and have begun to be interrogated to identify moderators of treatment. Genomic and phenotypic data from the UK BioBank [133, 134], which recruited 500,000 participants from the general population in the United Kingdom, are now publicly available. The Million Veteran Program [133], an effort of the U.S. Department of Veterans Affairs, has now recruited more than 700,000 veterans for whom genotypic and phenotypic information from questionnaires and the electronic health record [135], represents a valuable source of data for discovery. These efforts have begun to yield novel genetic loci implicated in alcohol consumption and alcohol-related problems [136] and more can be expected in the coming years.

Pharmacogenetic studies of AUD will benefit from larger, more diverse, and better characterized samples that can be followed longitudinally. Elucidation of the pathophysiology of AUD and identifying valid endophenotypes will enhance the discovery of genetic moderators of AUD treatment and allow the targeting of genetic and biobehavioral mechanisms. Ultimately, though, stakeholders (including basic and clinical researchers, clinicians, and clinical administrators must align their goals and resources [118, 130] to realize the fundamental goals of precision medicine as applied to AUD treatment.

Acknowledgments

Funding

This paper was funded by support from the Mental Illness Research, Education, and Clinical Center of the Veterans Integrated Service Network 4, U.S. Department of Veterans Affairs provided to E Hartwell and H Kranzler and by the NIAAA grants R01 AA023192 and R01 AA021164 provided to H Kranzler.

References

Papers of special note have been highlighted as:

* of interest

** of considerable interest

1. Center for Behavioral Health Statistics and Quality. Results from the 2016 National Survey on Drug Use and Health: detailed tables. https://www.samhsa.gov/data/sites/default/files/NSDUH-DetTabs-2016/NSDUH-DetTabs-2016.pdf
2. Grant BF, Goldstein RB, Saha TD, et al. Epidemiology of DSM-5 alcohol use disorder: results from the National Epidemiologic Survey on Alcohol and Related Conditions III. JAMA Psychiat. 2015;72(8):757–66.
3. Substance Abuse and Mental Health Services Administration. Key substance use and mental health indicators in the United States: results from the 2016 National Survey on Drug Use and Health. In: Center for Behavioral Health Statistics and Quality, Rockville 2017.
4. American Psychological Association. Diagnostic and Statistical Manual (5th ed.). Arlington, VA.
5. Han C, McGue MK, Iacono WG. Lifetime tobacco, alcohol and other substance use in adolescent Minnesota twins: univariate and multivariate behavioral genetic analyses. Addiction. 1999;94(7): 981–993. [PubMed: 10707437]
6. Verhulst B, Neale MC, Kendler KS. The heritability of alcohol use disorders: a meta-analysis of twin and adoption studies. Psychol Med. 2015;45(5):1061–72. [PubMed: 25171596]
7. Tawa EA, Hall SD, Lohoff FW. Overview of the genetics of alcohol use disorder. Alcohol Alcoholism. 2016;51(5):507–514. [PubMed: 27445363]
8. Dick DM, Kendler KS. The impact of gene-environment interaction on alcohol use disorders. Alcohol Res. 2012;34(3):318–24. [PubMed: 23134047]
9. Salvatore JE, Gottesman II, Dick DM. Endophenotypes for alcohol use disorder: an update on the field. Curr Addict Rep. 2015;2(1):76–90. [PubMed: 26236574]
10. Jones JD, Comer SD, Kranzler HR. The pharmacogenetics of alcohol use disorder. Alcohol Clin Exp Res. 2015;39(3):391–402. [PubMed: 25703505]
11. Chastain G Alcohol, neurotransmitter systems, and behavior. J Gen Psych. 2006;133(4):329–335. *Succint review of alcohol's impact on neurotransmitter systems.
12. Campbell AD, Kohl RR, McBride WJ. Serotonin-3 receptor and ethanol-stimulated somatodendritic dopamine release. Alcohol. 1996;13(6):569–74. [PubMed: 8949951]
13. Mark TL, Kassed CA, Vandivort-Warren R, et al. Alcohol and opioid dependence medications: prescription trends, overall and by physician specialty. Drug Alcohol Depend. 2009;99(1–3):345–9. [PubMed: 18819759]
14. Oliva EM, Maisel NC, Gordon AJ, et al. Barriers to use of pharmacotherapy for addiction disorders and how to overcome them. Curr Psychiatry Rep. 2011;13(5):374. [PubMed: 21773951]
15. Roman PM, Abraham AJ, Knudsen HK. Using medication-assisted treatment for substance use disorders: evidence of barriers and facilitators of implementation. Addict Behav. 2011;36(6):584–589. [PubMed: 21377275]
16. Kranzler HR, Soyka M. Diagnosis and pharmacotherapy of alcohol use disorder: a review. JAMA-J Am Med Assoc. 2018;320(8):815–824.*Good review of how to identify, diagnose, and intervene pharmacologically with patients who drink heavily.
17. Soyka M, Müller CA. Pharmacotherapy of alcoholism – an update on approved and off-label medications. Expert Opin Pharmaco. 2017;18(12):1187–1199.
18. van den Brink W, Sorensen P, Torup L, et al. Long-term efficacy, tolerability and safety of nalmefene as-needed in patients with alcohol dependence: a 1-year, randomised controlled study. J Psychopharmacol. 2014;28(8):733–44. [PubMed: 24671340]
19. Mann K, Bladstrom A, Torup L, et al. Extending the treatment options in alcohol dependence: a randomized controlled study of as-needed nalmefene. Biol Psychiatry. 2013;73(8):706–13. [PubMed: 23237314]

20. Gual A, He Y, Torup L, et al. A randomised, double-blind, placebo-controlled, efficacy study of nalmefene, as-needed use, in patients with alcohol dependence. Eur Neuropsychopharmacol. 2013;23(11):1432–1442. [PubMed: 23562264]
21. Agabio R, Leggio L. Baclofen in the treatment of patients with alcohol use disorder and other mental health disorders. Front Psychiatry. 2018;9:464–471. [PubMed: 30323774]
22. Walker LC, Lawrence AJ. Investigational drug therapies in phase I and phase II clinical trials for alcohol use disorders. Expert Opin Inv Drug. 2018;27(8):677–690. *Of interest for readers who want to see an extensive list of compounds under investigation
23. Anton RF, O'Malley SS, Ciraulo DA, et al. Combined pharmacotherapies and behavioral interventions for alcohol dependence: the COMBINE study: a randomized controlled trial. JAMA. 2006;295(17):2003–2017. * [PubMed: 16670409] Landmark study in AUD pharmacotherapy.
24. Jonas DE, Amick HR, Feltner C, et al. Pharmacotherapy for adults with alcohol use disorders in outpatient settings: a systematic review and meta-analysis. JAMA. 2014;311(18):1889–1900. [PubMed: 24825644]
25. Maisel NC, Blodgett JC, Wilbourne PL, et al. Meta-analysis of naltrexone and acamprosate for treating alcohol use disorders: when are these medications most helpful? Addiction. 2013;108(2): 275–293. [PubMed: 23075288]
26. Krystal JH, Cramer JA, Krol WF, et al. Naltrexone in the treatment of alcohol dependence. New Engl J Med. 2001;345(24):1734–1739. [PubMed: 11742047]
27. Haerian BS, Haerian MS. OPRM1 rs1799971 polymorphism and opioid dependence: evidence from a meta-analysis. Pharmacogenomics. 2013;14(7):813–824. [PubMed: 23651028]
28. Mague SD, Blendy JA. OPRM1 SNP (A118G): involvement in disease development, treatment response, and animal models. Drug Alcohol Depend. 2010;108(3):172–182. [PubMed: 20074870]
29. Oslin DW, Berrettini W, Kranzler HR, et al. A functional polymorphism of the μ-opioid receptor gene is associated with naltrexone response in alcohol-dependent patients. Neuropsychopharmacol. 2003;28(8):1546–1552.
30. Pettinati HM, Anton RF, Willenbring ML. The COMBINE Study: An Overview of the Largest Pharmacotherapy Study to Date for Treating Alcohol Dependence. Psychiatr. 2006;3(10):36–9.
31. Anton RF, Oroszi G, O'Malley S, et al. An evaluation of mu-opioid receptor (OPRM1) as a predictor of naltrexone response in the treatment of alcohol dependence: results from the Combined Pharmacotherapies and Behavioral Interventions for Alcohol Dependence (COMBINE) study. Arch Gen Psychiatry. 2008;65(2):135–44. [PubMed: 18250251]
32. Gelernter J, Gueorguieva R, Kranzler HR, et al. Opioid Receptor Gene (OPRM1, OPRK1, and OPRD1) Variants and Response to Naltrexone Treatment for Alcohol Dependence: Results From the VA Cooperative Study. Alcohol Clin Exp Res. 2007;31(4):555–563. [PubMed: 17374034]
33. Arias AJ, Gelernter J, Gueorguieva R, et al. Pharmacogenetics of naltrexone and disulfiram in alcohol dependent, dually diagnosed veterans. American J Addiction. 2014;23(3):288–293.
34. Cubells J, Zabetian C. Human genetics of plasma dopamine β-hydroxylase activity: applications to research in psychiatry and neurology. Psychopharmacol. 2004;174(4):463–476.
35. Foulds JA, Ton K, Kennedy MA, et al. OPRM1 genotype and naltrexone response in depressed alcohol-dependent patients. Pharmacogenet Genom. 2015;25(5):270–273.
36. Oslin DW, Leong SH, Lynch KG, et al. Naltrexone vs placebo for the treatment of alcohol dependence: A randomized clinical trial. JAMA Psychiatr. 2015;72(5):430–7. *Example of a well designed, prospective pharmacogenetic study of AUD.
37. Schacht JP, Randall PK, Latham PK, et al. Predictors of naltrexone response in a randomized trial: reward-related brain activation, OPRM1 genotype, and smoking status. Neuropsychopharmacol. 2017;42:2640–2653.
38. Coller JK, Cahill S, Edmonds C, et al. OPRM1 A118G genotype fails to predict the effectiveness of naltrexone treatment for alcohol dependence. Pharmacogenet Genom. 2011;21(12):902–905.
39. Arias A, Feinn R, Kranzler HR. Association of an Asn40Asp (A118G) polymorphism in the μ-opioid receptor gene with substance dependence: a meta-analysis. Drug Alcohol Depen. 2006;83(3):262–268.

40. Hernandez-Avila CA, Covault J, Wand G, et al. Population-specific effects of the Asn40Asp polymorphism at the mu-opioid receptor gene (OPRM1) on HPA-axis activation. Pharmacogenet Genomics. 2007;17(12):1031–8. [PubMed: 18004207]
41. Kim S-G, Kim C-M, Choi S-W, et al. A mu opioid receptor gene polymorphism (A118G) and naltrexone treatment response in adherent Korean alcohol-dependent patients. Psychopharmacolog. 2009;201(4):611–618.
42. Ray LA, Bujarski S, Chin PF, et al. Pharmacogenetics of naltrexone in Asian Americans: a randomized placebo-controlled laboratory study. Neuropsychopharmacol. 012;37(2):445–455.
43. Ray LA, Green R, Roche DJO, et al. Pharmacogenetic effects of naltrexone in individuals of East Asian descent: human laboratory findings from a randomized trial. Alcohol Clin Exp Res. 2018;42(3):613–623. [PubMed: 29265379]
44. Cservenka A, Yardley MM, Ray LA. Review: Pharmacogenetics of alcoholism treatment: Implications of ethnic diversity. Am J Addict. 2017;26(5):516–525. [PubMed: 28134463]
45. Ray LA, Hutchison KE. Effects of naltrexone on alcohol sensitivity and genetic moderators of medication response: a double-blind placebo-controlled study. Arch Gen Psychiatry. 2007;64(9): 1069–77. [PubMed: 17768272]
46. Ashenhurst JR, Bujarski S, Ray LA. Delta and kappa opioid receptor polymorphisms influence the effects of naltrexone on subjective responses to alcohol. Pharmacol Biochem Beh. 2012;103(2): 253–259.
47. Crist R, Ambrose-Lanci L, Vaswani M, et al. Case–control association analysis of polymorphisms in the delta-opioid receptor, OPRD1, with cocaine and opioid addicted populations. Drug Alcohol Depend. 2013;127(1–3):122–128. [PubMed: 22795689]
48. Nelson EC, Lynskey MT, Heath AC, et al. Association of OPRD1 polymorphisms with heroin dependence in a large case-control series. Addict Biol. 2014;19(1):111–121. [PubMed: 22500942]
49. Zhang H, Kranzler H, Yang B, et al. The OPRD1 and OPRK1 loci in alcohol or drug dependence: OPRD1 variation modulates substance dependence risk. Mol Psychiatr. 2008;13(5):531.
50. Setiawan E, Pihl RO, Cox SML, et al. The effect of naltrexone on alcohol's stimulant properties and self-administration behavior in social drinkers: influence of gender and genotype. Alcohol Clin Exp Res. 2011;35(6):1134–1141. [PubMed: 21410481]
51. Hutchison KE, Allen DL, Filbey FM, et al. CHRNA4 and tobacco dependence: from gene regulation to treatment outcome. Arch Gen Psychiatry. 2007;64(9):1078–86. [PubMed: 17768273]
52. McGeary JE, Monti PM, Rohsenow DJ, et al. Genetic moderators of naltrexone's effects on alcohol cue reactivity. Alcohol Clin Exp Res. 2006;30(8):1288–96. [PubMed: 16899031]
53. Caye A, Spadini AV, Karam RG, et al. Predictors of persistence of ADHD into adulthood: a systematic review of the literature and meta-analysis. Eur Child Adoles Psy. 2016;25(11):1151–1159.
54. McGeary J The DRD4 exon 3 VNTR polymorphism and addiction-related phenotypes: a review. Pharmacol Biochem Beh. 2009;93:222–229.
55. Lai JH, Zhu YS, Huo ZH, et al. Association study of polymorphisms in the promoter region of DRD4 with schizophrenia, depression, and heroin addiction. Brain Res. 2010;1359:227–232. [PubMed: 20801104]
56. Schmidt LA, Fox NA, Perez-Edgar K, et al. Linking Gene, Brain, and Behavior: DRD4, frontal asymmetry, and temperament. Psychol Sci. 2009;20:831–837. [PubMed: 19493320]
57. Chamorro AJ, Marcos M, Mirón-Canelo JA, et al. Association of μ-opioid receptor (OPRM1) gene polymorphism with response to naltrexone in alcohol dependence: a systematic review and meta-analysis. Addict Biol. 2012;17(3):505–512. [PubMed: 22515274]
58. Jonas DE, Amick HR, Feltner C, et al. Genetic polymorphisms and response to medications for alcohol use disorders: a systematic review and meta-analysis. Pharmacogenomics. 2014;15(13): 1687–1700. [PubMed: 25410894]
59. Schacht JP, Anton RF, Voronin KE, et al. Interacting effects of naltrexone and OPRM1 and DAT1 variation on the neural response to alcohol cues. Neuropsychopharmacol. 2013;38(3):414–22.
60. Ziauddeen H, Nestor LJ, Subramaniam N, et al. Opioid antagonists and the A118G polymorphism in the μ-opioid receptor gene: effects of GSK1521498 and naltrexone in healthy drinkers stratified by OPRM1 genotype. Neuropsychopharmacolo. 2016;41:2647–2657.

61. Boettiger CA, Kelley EA, Mitchell JM, et al. Now or Later? An fMRI study of the effects of endogenous opioid blockade on a decision-making network. Pharmacol Biochem Beh. 2009;93(3): 291–299.
62. Yoshimura A, Kimura M, Nakayama H, et al. Efficacy of disulfiram for the treatment of alcohol dependence assessed with a multicenter randomized controlled trial. Alcohol Clin Exp Res. 2014;38(2):572–578. [PubMed: 24117666]
63. Gross ER, Zambelli VO, Small BA, et al. A personalized medicine approach for Asian Americans with the aldehyde dehydrogenase 2*2 variant. Annu Rev Pharmacol. 2015;55:107–127.
64. Thompson A, Owens L, Pushpakom SP, et al. Pharmacotherapy for alcohol dependence: a stratified approach. Pharmacol Therapeut. 2015;153:10–24.
65. Ooteman W, Naassila M, Koeter MWJ, et al. Predicting the effect of naltrexone and acamprosate in alcohol-dependent patients using genetic indicators. Addict Biol. 2009;14(3):328–337. [PubMed: 19523047]
66. Karpyak V, Biernacka J, Geske J, et al. Genetic markers associated with abstinence length in alcohol-dependent subjects treated with acamprosate. Transl Psychiat. 2014;4(10):e453.
67. Kiefer F, Witt S, Frank J, et al. Involvement of the atrial natriuretic peptide transcription factor GATA4 in alcohol dependence, relapse risk and treatment response to acamprosate. harmacogenomics journal. 2011;11(5):368–374.
68. Karpyak VM, Winham SJ, Biernacka JM, et al. Association of GATA4 sequence variation with alcohol dependence. Addict Biol. 2014;19(2):312–315. [PubMed: 22862823]
69. Soyka M Nalmefene for the treatment of alcohol use disorders: recent data and clinical potential. Expert Opin Pharmaco. 2016;17(4):619–626.
70. Palpacuer C, Laviolle B, Boussageon R, et al. Risks and benefits of nalmefene in the treatment of adult alcohol dependence: a systematic literature review and neta-analysis of published and unpublished double-blind randomized controlled trials. PLoS Med. 2015;12(12):e1001924. [PubMed: 26694529]
71. Karhuvaara S, Simojoki K, Virta A, et al. Targeted nalmefene with simple medical management in the treatment of heavy drinkers: a randomized double-blind placebo-controlled multicenter study. Alcohol Clin Exp Res. 2007;31(7):1179–87. [PubMed: 17451401]
72. Arias AJ, Armeli S, Gelernter J, et al. Effects of opioid receptor gene variation on targeted nalmefene treatment in heavy drinkers. Alcohol Clin Exp Res. 2008;32(7):1159–1166. [PubMed: 18537939]
73. Blodgett JC, Del Re AC, Maisel NC, et al. A meta-analysis of topiramate's effects for individuals with alcohol use disorders. Alcohol Clin Exp Res. 2014;38(6):1481–1488. [PubMed: 24796492]
74. Skradski S, White HS. Topiramate blocks kainate-evoked cobalt influx into cultured neurons. Epilepsia. 2000;41:45–47.
75. Gibbs JW III, Sombati S, DeLorenzo RJ, et al. Cellular actions of topiramate: blockade of kainate-evoked inward currents in cultured hippocampal neurons. Epilepsia. 2000;41:10–16. [PubMed: 10643917]
76. Johnson BA, Rosenthal N, Capece JA, et al. Topiramate for treating alcohol dependence: a randomized controlled trial. JAMA. 2007;298(14):1641–51. [PubMed: 17925516]
77. Johnson BA, Ait-Daoud N, Bowden CL, et al. Oral topiramate for treatment of alcohol dependence: a randomised controlled trial. The Lancet. 2003;361:1677–1685.
78. Gryder DS, Rogawski MA. Selective antagonism of GluR5 kainate-receptor-mediated synaptic currents by topiramate in rat basolateral amygdala neurons. J Neurosci. 2003;23:7069–7074. [PubMed: 12904467]
79. Kaminski RM, Banerjee M, Rogawski MA. Topiramate selectively protects against seizures induced by ATPA, a GluR5 kainate receptor agonist. Neuropharmacol. 2004;46:1097–1104.
80. Sampaio AS, Fagerness J, Crane J, et al. Association between polymorphisms in GRIK2 gene and obsessive-compulsive disorder: a family-based study. CNS Neurosci Ther. 2011;17:141–7. [PubMed: 20370803]
81. Hirata Y, Zai CC, Souza RP, et al. Association study of GRIK1 gene polymorphisms in schizophrenia: case–control and family-based studies. Human Psychopharm Clin. 2012;27:345–351.

82. Lee J-H, Lee J-M, Ramos EM, et al. TAA repeat variation in the GRIK2 gene does not influence age at onset in Huntington's disease. Biochem Bioph Res Co. 2012;424(3):404–408.
83. Kranzler HR, Gelernter J, Anton RF, et al. Association of markers in the 3' region of the GluR5 kainate receptor subunit gene to alcohol dependence. Alcohol Clin Exp Res. 2009;33(5):925–30. [PubMed: 19320626]
84. Ray LA, Miranda R, MacKillop J, et al. A preliminary pharmacogenetic investigation of adverse events from topiramate in heavy drinkers. Exp Clin Psychopharm. 2009;17(2):122–129.
85. Kranzler HR, Covault J, Feinn R, et al. Topiramate Treatment for Heavy Drinkers: Moderation by a GRIK1 Polymorphism. Am J Psychiat. 2014;171(4):445–452. * [PubMed: 24525690] Promising pharmacogenetic finding from a well designed and executed study.
86. Feinn R, Curtis B, Kranzler HR. Balancing Risk and Benefit in Heavy Drinkers Treated with Topiramate: Implications for Personalized Care. J Clin Psychiat. 2016;77(3):e278–e282.
87. Kranzler HR, Wetherill R, Feinn R, et al. Posttreatment Effects of Topiramate Treatment for Heavy Drinking. Alcohol Clin Exp Res. 2014;38(12):3017–3023. [PubMed: 25581656]
88. Morley KC, Kranzler HR, Luquin N, et al. Topiramate versus naltrexone for alcohol use disorder: study protocol for a genotype-stratified, double-blind randomised controlled trial (TOP study). Trials. 2018;19(1):443. [PubMed: 30115121]
89. Kranzler HR, Armeli S, Tennen H, et al. A double-blind, randomized trial of sertraline for alcohol dependence: moderation by age of onset [corrected] and 5-hydroxytryptamine transporter-linked promoter region genotype. J Clin Psychopharmacol. 2011;31(1):22–30. [PubMed: 21192139]
90. Sachs BD, Dodson K. Chapter 18 - Serotonin deficiency and alcohol use disorders In: Watson RR, Zibadi S, editors. Addictive Substances and Neurological Disease: Academic Press; 2017 p. 181–189.
91. Kenna GA, Zywiak WH, Swift RM, et al. Ondansetron and sertraline may interact with 5-HTTLPR and DRD4 polymorphisms to reduce drinking in non-treatment seeking alcohol-dependent women: exploratory findings. Alcohol. 2014 9;48(6):515–22. [PubMed: 25212749]
92. Schadé A, Marquenie LA, van Balkom AJLM, et al. The effectiveness of anxiety treatment on alcohol-dependent patients with a comorbid phobic disorder: a randomized controlled trial. Alcohol Clin Exp Res. 2005;29:794–800. [PubMed: 15897725]
93. Pettinati HM, Volpicelli JR, Luck G, et al. Double-blind clinical trial of sertraline treatment for alcohol dependence. J Clin Psychopharmacol. 2001;21:143–53. [PubMed: 11270910]
94. Rossinfosse C, Wauthy J, Bertrand J. SSRI antidepressants and alcoholism. Rev Med Liege. 2000;55:1003–1010. [PubMed: 11195702]
95. Kenna GA. Medications acting on the serotonergic system for the treatment of alcohol dependent patients. Curr Pharmt Design. 2010;16(19):2126–2135.
96. Ait-Daoud N, Seneviratne C, Smith JB, et al. Preliminary evidence for cue-induced alcohol craving modulated by serotonin transporter gene polymorphism rs1042173. Front Psychiatr. 2012;3:6–11.
97. Kang H-J, Kim J-M, Stewart R, et al. Association of SLC6A4 methylation with early adversity, characteristics and outcomes in depression. Prog Neuro-Psychoph. 2013;44:23–28.
98. Koenen KC, Uddin M, Chang S-C, et al. SLC6A4 methylation modifies the effect of the number of traumatic events on risk for posttraumatic stress disorder. Depress Anxiety. 2011;28(8):639–647. [PubMed: 21608084]
99. Goldman N, Glei DA, Lin Y-H, et al. The serotonin transporter polymorphism (5-HTTLPR): allelic variation and links with depressive symptoms. Depress Anxiety. 2010;27(3):260–269. [PubMed: 20196101]
100. Strug LJ, Suresh R, Fyer AJ, et al. Panic disorder is associated with the serotonin transporter gene (SLC6A4) but not the promoter region (5-HTTLPR). Mol Psychiatr. 2008;15:166.
101. Bauer IE, Graham DP, Soares JC, et al. Serotonergic gene variation in substance use pharmacotherapy: a systematic review. Pharmacogenomics. 2015;16(11):1–8. [PubMed: 25560466]
102. Blackwell CP, Harding SM. The clinical pharmacology of ondansetron. Eur J Cancer Clin Oncol. 1989 1989;25 Suppl 1:S21–4; discussion S25–7.

103. Johnson BA, Ait-Daoud N, Seneviratne C, et al. Pharmacogenetic approach at the serotonin transporter gene as a method of reducing the severity of alcohol drinking. Am J Psychiat. 2011;168(3):265–275. [PubMed: 21247998]
104. Johnson BA, Seneviratne C, Wang X-Q, et al. Determination of genotype combinations that can predict the outcome of the treatment of alcohol dependence using the 5-HT3 antagonist ondansetron. Am J Psychiat. 2013;170(9):1020–1031. [PubMed: 23897038]
105. Kenna GA, Zywiak WH, Swift RM, et al. Ondansetron reduces naturalistic drinking in nontreatment-seeking alcohol-dependent individuals with the LL 5'-HTTLPR genotype: a laboratory study. Alcohol Clin Exp Res. 2014;38(6):1567–74. [PubMed: 24773166]
106. Agabio R, Sinclair JMA, Addolorato G, et al. Baclofen for the treatment of alcohol use disorder: the Cagliari Statement. Lancet Psychiatr. 2018.
107. Morley KC, Luquin N, Baillie A, et al. Moderation of baclofen response by a GABAB receptor polymorphism: results from the BacALD randomized controlled trial. Addiction. 2018;113(12): 2205–2213. [PubMed: 29968397]
108. Vlachou S, Markou A. GABAB Receptors in Reward Processes In: Blackburn TP, editor. Advances in Pharmacology. Vol. 58: Academic Press; 2010 p. 315–371. [PubMed: 20655488]
109. Fatemi SH, Folsom TD, Thuras PD. Deficits in GABAB receptor system in schizophrenia and mood disorders: A postmortem study. Schizophr Res. 2011;128(1):37–43. [PubMed: 21303731]
110. Heaney CF, Kinney JW. Role of GABAB receptors in learning and memory and neurological disorders. Neurosci Biobehav R. 2016;63:1–28.
111. D'Souza MS, Markou A. Neuronal mechanisms underlying development of nicotine dependence: implications for novel smoking-cessation treatments. Addiction Sc Clin Practice. 2011;6(1):4–16.
112. Palpacuer C, Duprez R, Huneau A, et al. Pharmacologically controlled drinking in the treatment of alcohol dependence or alcohol use disorders: a systematic review with direct and network meta-analyses on nalmefene, naltrexone, acamprosate, baclofen and topiramate. Addiction. 2018 2;113(2):220–237. [PubMed: 28940866]
113. Ray LA, Bujarski S, Yardley MM, et al. Differences between treatment-seeking and non-treatment-seeking participants in medication studies for alcoholism: do they matter? Am J Drug Alcohol Ab. 2017:1–8.
114. Rohn MC, Lee MR, Kleuter SB, et al. Differences between treatment-seeking and nontreatment-seeking alcohol-dependent research participants: an exploratory analysis. Alc Clin Exp Res. 2017;41(2):414–420.
115. Oliver JA, McClernon FJ. Precision medicine in addiction research: where has the time gone? Addiction. 2017;112(12):2096–2097. * [PubMed: 29105925] Informative review of current areas of relevance to precision medicine in addiction treatment.
116. Pettinati HM, Weiss RD, Dundon W, et al. A structured approach to medical management: a psychosocial intervention to support pharmacotherapy in the treatment of alcohol dependence. J Stud Alcohol, Supplement. 2005 (s15):170–178.
117. Miller PM, Book SW, Stewart SH. Medical treatment of alcohol dependence: a systematic review. Int J Psychiatry Med. 2011;42(3):227–66. [PubMed: 22439295]
118. van der Stel J Precision in addiction care: does it make a difference? Yale J Biol Med. 2015;88(4): 415–422. [PubMed: 26604867]
119. Baurley JW, McMahan CS, Ervin CM, et al. Biosignature discovery for substance use disorders using statistical learning. Trends Mol Med. 2018;24(2):221–235. [PubMed: 29409736]
120. Witkiewitz K, Kranzler HR, Hallgren KA, et al. Drinking risk level reductions associated with improvements in physical health and quality of life among individuals with alcohol use disorder. Alc Clin Exp Res. 2018;42(12):2453–2465.
121. Roche DJ, Ray LA. Subjective response as a consideration in the pharmacogenetics of alcoholism treatment. Pharmacogenomics. 2015;16(7):721–736. [PubMed: 25950242]
122. Mann K, Roos CR, Hoffmann S, et al. Precision medicine in alcohol dependence: a controlled trial testing pharmacotherapy response among reward and relief drinking phenotypes. Neuropsychopharmacolog. 2017;43:891–899.
123. Hall KT, Loscalzo J, Kaptchuk TJ. Genetics and the placebo effect: the placebome. Trends Mol Med. 2015;21(5):285–294. [PubMed: 25883069]

124. Colagiuri B, Schenk LA, Kessler MD, et al. The placebo effect: from concepts to genes. Neuroscience. 2015;307:171–190. [PubMed: 26272535]

125. Ray LA, Barr CS, Blendy JA, et al. The role of the Asn40Asp polymorphism of the nu opioid receptor gene (OPRM1) on alcoholism etiology and treatment: a critical review. Alcohol Clin Exp Res. 2012;36(3):385–394. [PubMed: 21895723]

126. Hart AB, Kranzler HR. Alcohol dependence genetics: lessons learned from genome-Wide association studies (GWAS) and post-GWAS analyses. Alcohol Clin Exp Res. 2015;39(8):1312–1327. [PubMed: 26110981]

127. Gelernter J, Kranzler HR, Sherva R, et al. Genome-wide association study of alcohol dependence:significant findings in African- and European-Americans including novel risk loci. Mol Psychiatr. 2013;19:41–49.

128. Walters RK, Adams MJ, Adkins AE, et al. Trans-ancestral GWAS of alcohol dependence reveals common genetic underpinnings with psychiatric disorders. bioRxiv. 2018:257311 (preprint).

129. Seneviratne C, Johnson BA. Advances in medications and tailoring treatment for alcohol use disorder. Alcohol Res Curr Rev. 2015;37(1):15–28.

130. Kranzler HR, Smith RV, Schnoll R, et al. Precision medicine and pharmacogenetics: what does oncology have that addiction medicine does not? Addiction. 2017;112(12):2086–2094. * [PubMed: 28431457] Excellent review of why addiction medicine lags behind oncology and cardiology in the clinical application of precision medicine.

131. Ikediobi ON. Somatic pharmacogenomics in cancer. Pharmacogenomics J. 2008;8:305. [PubMed: 18679398]

132. Williams EC, Young JP, Achtmeyer CE, et al. Primary care providers' interest in using a genetic test to guide alcohol use disorder treatment. J Subst Abuse Treat. 2016;70:14–20. [PubMed: 27692183]

133. Gaziano JM, Concato J, Brophy M, et al. Million Veteran Program: a mega-biobank to study genetic influences on health and disease. J Clin Epidemiol. 2016;70:214–223. * [PubMed: 26441289] This article nicely orients the reader to big datasets and the implications they have for advances in precision medicine.

134. Allen N, Sudlow C, Downey P, et al. UK Biobank: Current status and what it means for epidemiology. Health Policy Techn. 2012;1(3):123–126.

135. Roden D, Denny J. Integrating electronic health record genotype and phenotype datasets to transform patient care. Clin Pharmacol Ther. 2016;99(3):298–305. [PubMed: 26667791]

136. Clarke TK, Adams MJ, Davies G, et al. Genome-wide association study of alcohol consumption and genetic overlap with other health-related traits in UK Biobank (N=112 117). Mol Psychiatr. 2017;22:1376.

Table 1.

Pharmacogenetic studies of naltrexone for treating alcohol use disorder.

Reference	SNP(s)	N	Population Group	Diagnosis	Effect
Oslin et al. (2003)[1]	rs1799971	141	European Americans	Alcohol dependence	Asp40 carriers treated with naltrexone had a lower rate and a longer time to relapse to heavy drinking.
Anton et al. (2008)[2]	rs1799971	604	European Americans	Alcohol dependence	Asp40 carriers treated with naltrexone had a lower percentage of heavy drinking days and greater likelihood of "good clinical outcome."
Gelernter et al. (2007)[2]	rs1799971 and 5 other opioid receptor SNPs	215	European and African Americans	Alcohol dependence	No SNP x medication interaction for any of the 6 SNPs examined.
Kim et al. (2009)[3]	rs1799971	63	Korean	Alcohol dependence	Asp40 carriers had a lower rate and a longer time to relapse to heavy drinking.
Ooteman et al. (2009)[4]	rs1799971; SNPs in *DRD2*, *GABRA6*, and *GABRA2*	108	Dutch	Alcohol dependence	No gene x medication effect
Coller et al. (2011)[3]	rs1799971	100	Australian	Alcohol dependence	No gene x time effect
Arias et al. (2014)[5]	rs1799971; rs1611115 in *DBH*	107	European Americans	Alcohol dependence with comorbid Axis I disorder	No gene x medication interaction. T-allele carriers of *DBH* reported less heavy drinking when treated with naltrexone.
Foulds et al. (2015)[3]	rs1799971	108	European and Maori descent	Alcohol dependence with major depression	No gene x medication interaction
Oslin et al. (2015)[6]	rs1799971	221	Predominately European Americans	Alcohol dependence	No gene x medication interaction
Schacht et al. (2017)[6]	rs1799971	152	European Americans and Asian Americans	Alcohol dependence	No gene x medication interaction. Asp40 carriers treated with naltrexone had a more rapid return to heavy drinking after treatment ended.

[1] Secondary analysis of 3 separate trials

[2] Secondary analysis of a larger, placebo-controlled trial

[3] Open-label, no control group

[4] Open-label comparison of naltrexone and acamprosate

[5] Secondary analysis of randomized trial comparing naltrexone, placebo, disulfiram or disulfiram with naltrexone

[6] Placebo-controlled, with randomization stratified on genotype