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REVIEW

On the path toward personalized medicine: implications of pharmacogenetic studies of alcohol use disorder medications

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ABSTRACT

Introduction: The heritability of alcohol use disorder (AUD) is estimated to be ~50%; however, the genetic basis of the disease is still poorly understood. The genetic variants identified thus far only explain a small percentage of AUD phenotypic variability. While genome-wide association studies (GWAS) are impacted by technical and methodological limitations, genetic variants that have been identified independently of GWAS findings can moderate the efficacy of AUD medications.

Areas covered: This review discusses findings from clinical pharmacogenetic studies of AUD medications. While the pharmacogenetic studies reviewed involve several genetic variants in the major neurotransmitter systems, genetic loci in the opioid system have garnered the most attention.

Expert opinion: The clinical utility of pharmacogenetics in AUD populations is uncertain at this time. There are several ongoing prospective clinical trials that will enhance knowledge regarding the applicability of pharmacogenetics in clinical populations. We recommend that future work in this area considers reverse translating from genotype to phenotype, mapping genes to stages of the addiction cycle, mapping genes to neural circuits, and harnessing large population-based cohorts.

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1. Introduction

Alcohol use disorder (AUD) is a chronic relapsing condition that is diagnosed when individuals present with at least two of eleven criteria related to tolerance to the subjective effects of alcohol, alcohol withdrawal symptoms, impaired control over alcohol use, alcohol craving, and impairments in psychosocial domains [1]. According to the 2015 National Survey on Drug Use and Health, 15.1 million adults in the United States had an AUD diagnosis [2]. In addition, alcohol use is the third leading preventable factor contributing to death in the U.S [3], with an estimated economic cost of ~$249 billion [4]. Although pathological alcohol consumption incurs substantial individual and societal costs, only a small subset (~10%) of people with AUD are treated [2].

Despite the high prevalence of AUD in the United States, there are only three FDA-approved pharmacological treatments for AUD. Disulfiram is the oldest medication for AUD, approved by the FDA in 1948 [5]. Its mechanism of action involves inhibition of aldehyde dehydrogenase, the enzyme responsible for converting acetaldehyde to acetate during alcohol metabolism, which leads to the accumulation of acetaldehyde after alcohol intake [6]. Elevated levels of acetaldehyde cause an aversive reaction deterring further alcohol use [7]. Acamprosate shares similarities with several amino acids, such as glutamate, GABA, aspartate, glycine, and taurine [8]. Acamprosate may normalize a hyper-glutamatergic state caused by extensive alcohol use and repeated phases of alcohol withdrawal, restoring the balance between inhibitory and excitatory neurotransmitters, and thus, attenuating alcohol craving [9]. However, acamprosate's exact mechanism of action is still unknown. Lastly, naltrexone (NTX) is available in both oral or extended-release injectable formulations. NTX is believed to inhibit alcohol-induced dopamine release in the nucleus accumbens, a key structure in the brain's reward system, with its behavioral effects being reduced subjective reward after drinking [10]. Unfortunately, medications for AUD show modest efficacy at best [5] with relapse rates ~50% 3 years after treatment onset [11,12]. Given that AUD is a heterogenous and complex syndrome, the one size fits all approach to treatment has had little success for this disorder relative to other medical conditions. Furthermore, medications development for AUD is marked by a host of challenges across the development spectrum, from preclinical studies to clinical trials [13]. Thus, it is important to identify individual factors that can improve the efficacy of treatments currently available and under investigation.

The role of genetics in AUD was founded on many years of observations that pathological alcohol consumption is clustered in families. Twin and adoption studies consistently find that the heritability of AUD is between 50% and 60% [14]; thus, transmission of risk alleles independent of environment may contribute to AUD etiology. While family, twin, and adoption studies provide initial evidence of an inherited risk of AUD, they cannot conclusively determine the role of genes in disease states. To address this issue, genetic linkage studies

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use a family-based method to evaluate whether one or more genetic markers spaced across the 23 chromosomes co-segregate with a disorder. The Collaborative Study on the Genetics of Alcoholism (COGA) was one of the first studies to utilize this novel genome-wide scan to map and characterize genetic variants that contribute to AUD [15]. With over nine research sites and an initial sample of 105 families and 987 individuals, COGA found that loci located on chromosomes 1, 7, and 3 linked with AUD, while different loci on chromosome 2 both linked with and were protective of AUD [16]. There are several limitations to linkage studies. For instance, these studies are labor-intensive because they require compilation of extended pedigrees. In addition, linkage studies offer poor genomic resolution because large chromosomal regions identified can contain several possible candidate genes.

Another approach involves genetic association in family-based and population samples. Compared to linkage designs, association studies are allele-based rather than locus-based. Association studies identify alleles of a gene that are more common in a person with a disease versus those without. COGA has conducted several candidate gene studies which have identified more than a dozen genes that associate with AUD and certain endophenotypes [17,18]. Risk alleles that contribute to AUD vulnerability involve major neurotransmitter systems, alcohol metabolism, neuropeptide signaling, neuroendocrine signaling, other signaling molecules, and cellular architecture [17,19]. Interestingly, the most replicable findings have been genetic variations in alcohol-metabolizing genes and protective effects on risk for AUD, especially in Asian populations. Importantly, these studies require a biologically relevant candidate gene or pathway to test for association with AUD. Because a priori knowledge is required, this limits the potential of finding novel and unexpected genetic associations. Overall, candidate gene association studies explain a small percentage of genetic variance and their lack of utility was recently underscored in [20].

Genome-wide association studies (GWAS) represent a discovery-based approach wherein an array of common single-nucleotide polymorphisms (SNPs) is examined across the entire genome without a priori hypothesis about a specific gene or pathway. Over the last several years, GWAS studies have found that variation in the genes encoding the alcohol-metabolizing enzymes is among the common variants with the largest effect on AUD risk [14]. Table 1 provides a review of prominent GWAS of AUD completed across racially and ethnically diverse populations. As can be seen in Table 1, sample sizes increase with recency of publication and the associations found in the alcohol-metabolizing enzyme genes represent the most consistent overall findings for GWAS of AUD to date [21], replicating findings from candidate gene and linkage studies. However, these results were somewhat discouraging because it was expected that GWAS would identify novel and unexpected variants that would enhance our understanding of the genetics of complex traits including AUD. Large sample sizes are required to achieve statistical power to detect small effects, especially for complex diseases, such as psychiatric disorders. In addition, very conservative statistical corrections are required to control for multiple testing of the more than 1 million SNPs that are investigated in a single GWAS. A Bonferroni-corrected genome-wide significance threshold set at $p < 10^{-8}$ is typically required. Furthermore, the heritability explained by SNP associations is less than estimates of heritability derived from family studies. The variants that reach statistical significance typically explain only a small fraction of the heritability, a phenomenon commonly referred to as 'missing heritability' [22]. Several hypotheses have been put forward to explain missing heritability, such as undetected rare variants of large effect, epistatic interactions, and the notion that heritability estimates from family studies may be overinflated [23–26].

It is well established that AUD risk is the result of multiple genes, environmental factors, and interactions across genes and gene x environment. To account for multiple genetic markers simultaneously, polygenic risk scores can be estimated from GWAS data and provide a quantitative measure of the cumulative effects of common genetic variance across the entire genome on risk for a disorder. Risk scores are calculated as a weighted sum of the number of risk alleles at the selected SNPs carried by a person. The weight is obtained from the effect size associated with the SNPs. These scores can be compared between persons and phenotypes. Polygenic risk scores have had some success in predicting AUD risk in individuals [27]; however, a recent genome-wide meta-analysis of AUD showed that these scores only explained between 0.3% and 1.7% of the variance in alcohol use and misuse phenotypes [28].

The GWAS approach is beginning to uncover novel biology contributing to the risk of AUD but will require larger samples and independent replication. Importantly, recent GWAS and meta-analytic studies find that the genetic underpinnings of AUD are distinct from alcohol consumption [29,30]. While an in-depth analysis of findings from GWAS of AUD and alcohol behaviors is beyond the scope of this review, the reader is referred to excellent reviews on the topic [31–33]. A comprehensive understanding of the genetic contribution of AUD may reveal potential targets for new pharmacotherapies as well as opening avenues for personalized medicine. The purpose of this qualitative review is to synthesize the findings of several studies that have examined genetic biomarkers in the context of pharmacotherapies for the treatment of AUD. Relevant published papers were identified using the PubMed database with the following keywords: 'pharmacogenetics, alcohol, and clinical trial.' The reference section of some papers was also used to identify pertinent papers. Studies were included if they assessed the moderating effects of genotypes on medication efficacy in the context of randomized clinical trials. Human laboratory studies were also included to provide background information where appropriate. Given the large correspondence between the DSM-IV diagnosis of alcohol dependence and DSM-5 moderate and severe diagnoses of AUD [34], we use the term AUD as a proxy for alcohol dependence detected using previous editions of the DSM. Future directions for pharmacogenetics of AUD are also discussed.

2. Pharmacogenetic studies of AUD medications

2.1. Pharmacogenetic studies involving the endogenous opioid system

Most clinical pharmacogenetic studies of AUD have focused on genetic variants in the endogenous opioid system, specifically postsynaptic receptors. Opioid ligands and receptors are widely dispersed throughout the central nervous system. As

Table 1. Findings from genome-wide association studies of AUD.

Discovery Sample	AUD Phenotype	SNPs identified ($P< 5 X 10^{-8}$)	Reference
German sample (men) 1,024 cases 996 controls	Case-control status	rs7590720 & rs1344694 (*PECR*)	(Treutlein et al., 2009) [95]
SAGE sample: 1,235 EA AD cases 1433 EA controls 662 AA AD cases 499 AA controls	Case-control status	None	(Bierut et al., 2010) [96]
COGA sample 847 EA AD cases 552 EA controls 345 AA AD cases 140 AA controls	Case-control status	None	(Edenberg et al.,2010) [97]
MGS2 control sample: 2,357 EAs 812 AAs	Criterion factor score	None	(Kendler et al., 2011) [98]
Australian sample: 2,062 AD cases 3,393 controls	(1) Case–control status (2) Quantitative factor score (3) Quantitative 'heaviness of drinking' factor score	None	(Heath et al., 2011) [99]
German sample (men) 1,333 severe AD cases 2,168 controls	Case-control status	rs1789891 (*ADH1C*)	(Frank et al., 2012) [100]
COGA and SAGE meta-analysis: 1,409 EA AD cases 1,518 EA controls 681 AA AD cases 608 AA controls	Case-control status	None	(Zuo et al., 2012) [101]
COGA sample: 2,322 EAs	DSM-IV criterion count	None	(Wang et al., 2013) [102]
MCTFR sample: 7,188 EAs	Factor score	None	(McGue et al., 2013) [103]
Korean sample: 117 AD cases 279 controls	Case-control status	rs1442492 & rs10516441 (*ADH7*); rs671 (*ALDH2*)	(Park et al., 2013) [104]
Chinese sample (male): 102 AD cases 212 controls	Case-control status	rs3782886 & rs671 (*ALDH2*)	(Quillen et al., 2014) [105]
Yale-Penn sample: 2,379 EA 3,318 AA SAGE sample: 2,752 EAs 1,311 AAs	DSM-IV criterion count; Case-control status	Combined meta-analysis: Ordinal rs17028615 (located on Chr. 4) rs28542574 (located on Chr. 4) rs2066702 & rs1229984 (*ADH1B)* Combined meta-analysis: Case-control rs1437396 (located on Chr. 2) rs1229984 (*ADH1B)*	(Gelernter et al., 2014) [106]
Meta-analysis and independent sample: 11,569 EA cases 34,999 EA controls 3,335 AA cases 2,945 AA controls	Case-control status	EAs: rs1229984 & rs3811802 (*ADH1B*) AAs: rs2066702 (*ADH1B*)	(Walters et al., 2018) [28]
MVP sample: 34,658 EA cases 167,346 EA controls 17,267 AA cases 39,381 AA controls 3,449 LA cases 10,726 LA controls 164 EAA cases 1,210 EAA controls 46 SAA cases 144 SAA controls	Case-control status	Trans-population Meta-analysis: rs1229984 (*ADH1B*)* rs1612735 (*ADH1C*)* rs5860563 (*ADH4*) rs1260326 (*GCKR*)* rs540606 (*SIX3*) rs13107325 (*SLC39A8*)* rs61902812 & rs4936277 (*DRD2*) rs7906104 (located on Chr. 10) rs1421085 (*FTO*)* *Loci significant in both AUDIT-C and AUD GWASs	(Kranzler et al., 2019) [29]
COGA sample: 880 AA Cases 951 AA Controls 2411 EA Cases 2438 EA Controls	Case-control status; DSM-IV criterion count; DSM-IV individual criteria	DSM-IV AUD Diagnoses (EA + AA): rs1229984 (*ADH1B*) rs61826952 (*RABGAP1L*)	(Lai et al., 2019) [107]
Han Chinese sample: 533 AD Cases 2848 Controls	Case-control status	rs1229984 (*ADH1B*) rs671 (*ALDH2*)	(Sun et al., 2019) [108]

AUD, Alcohol Use Disorder; AD, Alcohol Dependent; SNP, Single-Nucleotide Polymorphism; SAGE, Study of Addiction: Genetics and Environment; COGA, Center of Genetics of Alcoholism; MSG2, Molecular Genetics of Schizophrenia; MCTFR, Minnesota Center for Twin and Family Research; MVP, Million Veteran Program EA, European American; AA, African American; LA, Latino American; EAA, East Asian American; SAA, South Asian American; *PECR*, Peroxisomal Trans-2-Enoyl-CoA Reductase; *ADH*, Alcohol Dehydrogenase; *ALDH*, Aldehyde Dehydrogenase; *GCKR*, Glucokinase Regulator; *DRD2*, Dopamine Receptor D2; *SIX3*, SIX Homeobox 3; *SLC39A8*, Solute Carrier Family 39 Member 8; *FTO*, Alpha-Ketoglutarate Dependent Dioxygenase; *RABGAP1L*, RAB GTPase Activating Protein 1 Like; AUDIT-C, Alcohol Use Disorders Identification Test-Consumption.

such, they are involved in many biological processes, such as pain sensitivity, hormone secretion, reward, and the stress response. There are four main types of opioid receptors found in the mammalian central nervous system: mu, kappa, delta, and nociception/orphanin. Opioid receptors are G-coupled protein receptors that mainly interact with alpha-subunits of the Gi/o family. The Gi/o-alpha subunit typically inhibits adenylyl cyclase and reduces cyclic adenosine monophosphate, which in turn can decrease neuronal excitability and the activity of cellular phosphatases and kinases. Thus, activation of each of the receptor subtypes generally results in postsynaptic inhibition.

Several families of endogenous opioid peptides bind to these receptors, but the primary ligands are the endorphins, dynorphins, and enkephalins. These three families of peptides have varying degrees of affinity for each of the opioid receptors and none bind to only one receptor subtype. β-endorphins are derived from pro-opiomelanocortin (POMC) and are the primary ligands for the mu-opioid receptor, dynorphins for the kappa-opioid receptors, enkephalins for the delta-opioid receptors, and the peptides nociceptin and orphanin bind to nociceptin/orphanin receptors. It is currently posited that NTX works by occupying mu-opioid receptors preventing the binding of endogenous opioid peptides (e.g., β-endorphin) that are released upon alcohol intake [35], which in turn prevents GABA-mediated release of dopamine in the ventral tegmental area thereby blocking alcohols reinforcing effects [36,37].

As can be seen from Table 2, the most widely studied personalized medicine effect has been for NTX and *OPRM1* A118G genotype [38]. This SNP (rs1799971) in the mu-opioid receptor gene (*OPRM1*) causes an adenine to guanine substitution, altering the amino acid sequence of the receptor and may result in a gain of function of the receptor [39]. In human laboratory studies, G carriers showed greater subjective responses to alcohol, such as greater self-reported feelings of intoxication, stimulation, sedation, and happiness [40]. G carriers who were also heavy drinkers reported greater alcohol-induced craving in a cue reactivity task [41] and self-administered more alcohol relative to A homozygotes [42]. Neuroimaging studies have also reported differences in brain activation and dopamine release. Specifically, G carriers had greater brain activation in the striatum and orbitofrontal cortex in response to alcohol taste [43], while frontostriatal connectivity was reduced [44]. In addition, male G carriers showed increased dopamine release in the striatum following intravenous alcohol self-administration [45].

The findings on whether A118G polymorphisms moderate clinical outcomes have been mixed. Oslin et al. [46] were the first to show that G carriers had lower rates of relapse to heavy drinking and longer time to return to heavy drinking when treated with NTX relative to A homozygotes. Secondary analyses on data from the COMBINE study also showed better clinical outcomes in G carriers. Specifically, G carriers treated with NTX reported fewer heavy drinking days relative to placebo and A homozygotes who were treated with either NTX or placebo [47]. Additionally, G carriers treated with NTX had better clinical outcomes relative to A homozygotes treated with NTX [47]. However, it is important to note that this *OPRM1* SNP did not moderate clinical or neuroimaging outcomes in several investigations using the opioid antagonists NTX [48–54] and nalmefene [55], disulfiram [54] or acamprosate [49]. In a similar vein, G carriers may have greater susceptibility to relapse once off NTX [53]. While most findings discussed above were from retrospective studies, two randomized clinical trials that prospectively examined the moderating effect of the A118G SNP on responses to NTX failed to find an effect [51,53]. Interestingly, recent work has predicted naltrexone response using a self-report-based 'reward drinking' phenotype, which theoretically overlaps with this genetic profile [56].

Genetic variations in the kappa- and delta-opioid receptor genes (*OPRK1* and *OPRD1*, respectively) have also been investigated as potential moderators of opioid antagonist treatment, albeit to a lesser extent than to *OPRM1*. Kappa-opioid receptor activation as a result of escalated alcohol consumption and withdrawal contributes to the development of a negative emotional state [14]. Ashenhurst et al. [57] showed that an *OPRK1* non-coding SNP (rs997917) resulted in NTX–induced changes in alcohol sedation. Specifically, T homozygotes reported dampened alcohol sedation after NTX versus placebo, and relative to C carriers. Another *OPRK1* SNP (rs963549) did not moderate clinical outcomes in investigations using NTX [48] or nalmefene [55]. Like the mu-opioid receptor, alcohol also increases binding of endogenous opioids to delta-opioid receptors leading to increases in dopamine transmission [58]. The *OPRD1* SNP (rs465327) has also been shown to moderate NTX responses in the laboratory. A carrier treated with NTX reported lower alcohol-induced stimulation and reduced alcohol craving compared to NTX-treated G homozygotes [57]. Other *OPRD1* SNPs (rs2234918 and rs678849) did not moderate treatment responses to NTX [48] or nalmefene [55]. In summary, genetic variation in genes encoding the opioidergic system has received attention as possible moderators of behavioral and clinical responses to opioid antagonists, most notably naltrexone. However, the results of such studies have not been conclusive, particularly regarding a large prospective trial of naltrexone for AUD treatment based on *OPRM1* A118G SNP status [51]. While the experimental medicine work was robustly in favor of a pharmacogenetic effect [45,59,60], null findings [61] and effects in the opposite direction [62] were also reported. Nevertheless, it is possible that the pharmacogenetic signal found in tightly controlled experimental medicine models is not strong enough to be detected in clinical care, wherein samples and settings are more diverse.

2.2. Pharmacogenetic studies involving the serotonin system

Dysfunctions in serotonin signaling are implicated in early-onset AUD [14]. Variants in genes encoding serotonin transporters and receptors have been shown to moderate potential pharmacological treatments for AUD (see Table 2), such as selective-serotonin reuptake inhibitors (sertraline) and serotonin receptor antagonists (ondansetron). A repeat insertion polymorphism in the promoter region (5-HTTLPR) of the serotonin transport gene, *SLC6A4*, results in long (L) and short (S) alleles [63]. These alleles differentially modulate serotonin uptake in the synapse, with the result being a greater density of receptors and, thus, higher reuptake activity in L allele carriers relative to S-allele carriers. Thus, blockade of this

Table 2. Pharmacogenetic clinical trials of AUD medications.

Gene	Variant	Medication (Dosage)/	Medication Duration	Study Design/ Sample	Medication X Genetic Interaction	Reference [#]
Pharmacogenetic studies involving the opioid system						
OPRM1	rs1799971	NTX (50–100 mg/day)	12 weeks	RCT; AUD participants: 82 NTX 59 Placebo	G carriers: Lower relapse rates and longer time to return to HD	(Oslin et al., 2003) [46]
	rs1799971; rs17180961; rs648893	NTX (50 mg/day)	13 weeks	RCT; AUD participants: 149 NTX 64 Placebo	None	(Gelernter et al., 2007) [48]
	rs1799971	NTX (100 mg/day)	16 weeks	RCT; AUD participants: 301 NTX 303 Placebo	G carriers: Decreased % of HDD and greater % days abstinent	(Anton et al., 2008) [47]
	rs1799971	Nalmefene (40 mg/day)	28 weeks	RCT; HD participants; 166 Nalmefene 106 Placebo	None	(Arias et al., 2008) [55]
	rs1799971	NTX (50 mg/day)	12 weeks	Open-label trial; Korean AUD participants 32 NTX	G carriers: Longer time to relapse	(Kim et al., 2009) [109]
	rs1799971	NTX (50 mg/day); Acamprosate (1.3–2.0 g/day)	3 weeks	RCT; AUD participants: 52 NTX 56 Acamprosate	None	(Ooteman et al., 2009) [49]
	rs1799971	NTX (50 mg/day)	12 weeks	Open-label trial; AUD Australian participants: 100 NTX	None	(Coller et al., 2011) [50]
	rs1799971	NTX (50 mg/day)	2 weeks	RCT; Problem drinkers: 81 NTX 77 Placebo	G carriers: Attenuation of desire to drink in the evening but no effects on drinking outcomes	(Kranzler et al., 2013) [110]
	rs1799971	NTX (50 mg/day); Disulfiram (250 mg/day)	12 weeks	RCT; AUD participants: 44 NTX 48 Placebo 10 Disulfiram 14 Placebo	None	(Arias et al., 2014) [54]
	rs1799971	NTX (50 mg/day)	12 weeks	RCT: AUD participants: 111 NTX 110 Placebo	None	(Oslin et al., 2015) [51]
	rs1799971	NTX (50–100 mg/day)	12 weeks	Open-label trial; AUD + MDD participants; 108 NTX	None	(Foulds et al., 2015) [52]
	rs1799971	NTX (50 mg/day)	16 weeks	RCT; AUD participants: 73 NTX 73 Placebo	G carriers: Accelerated return to heavy drinking after treatment	(Schacht et al., 2017) [53]
OPRK1	rs963549	NTX (50 mg/day)	13 weeks	RCT; AUD males: 149 NTX 64 Placebo	None	(Gelernter et al., 2007) [48]
	rs963549	Nalmefene (40 mg/day)	28 weeks	RCT; HD participants; 166 Nalmefene 106 Placebo	None	(Arias et al., 2008) [55]
OPRD1	rs678849; rs2234918	NTX (50 mg/day)	13 weeks	RCT; AUD males: 149 NTX 64 Placebo	None	(Gelernter et al., 2007) [48]
	rs2234918; rs678849	Nalmefene (40 mg/day)	28 weeks	RCT; HD participants; 166 Nalmefene 106 Placebo	None	(Arias et al., 2008) [55]
Pharmacogenetic studies involving the serotonin system						
SLC6A4	5-HTTLPR;	Sertraline (200 mg/day)	12 weeks	RCT; AUD participants: 63 Sertraline 71 Placebo	LL homozygotes: Less drinking and heavy drinking days in late-onset/low vulnerability AUD individuals	(Kranzler et al., 2011) [66]

(*Continued*)

Table 2. (Continued).

Gene	Variant	Medication (Dosage)/	Medication Duration	Study Design/ Sample	Medication X Genetic Interaction	Reference [#]
	5-HTTLPR; rs1042173	Ondansetron (4 μg/kg/BID	11 weeks	RCT; AUD participants: 140 Ondansetron 143 Placebo	LL homozygotes: fewer drinks per drinking day and greater % days abstinent LL/TT genotype: fewer drinks per drinking day and greater % days abstinent vs other genotypes	(Johnson et al., 2011) [67]
HTR3A	rs1150226; rs1176713	Ondansetron (4 μg/kg/BID	11 weeks	RCT; AUD participants: 133 Ondansetron 138 Placebo	AG or GG genotypes: Fewer drinking days, fewer % heavy drinking days, & more days abstinent Medication effects were enhanced in individuals who possessed one or more of the *HTR3A* or *HTR3B* genotypes, along with the *SLC6A4*-LL/TT genotype	(Johnson et al., 2013) [68]
HTR3B	rs17614942	Ondansetron (4 μg/kg/BID	11 weeks	RCT; AUD participants: 133 Ondansetron 138 Placebo	AC genotype: Fewer drinking days, fewer % heavy drinking days, & more days abstinent Medication effects were enhanced in individuals who possessed one or more of the *HTR3A* or *HTR3B* genotypes, along with the SLC6A4-LL/TT genotype	(Johnson et al., 2013) [68]
Pharmacogenetic studies involving catecholamine systems						
DBH	rs1611115	NTX (50 mg/day); Disulfiram (250 mg/day)	12 weeks	RCT; AUD EA participants: 44 NTX 48 Placebo 10 Disulfiram 14 Placebo	T carriers: Higher rates of abstinence from HD on NTX CC homozygotes: Fewer drinks per drinking days on disulfiram	(Arias et al., 2014) [54]
DRD1	rs686	NTX (50 mg/day); Acamprosate (1.3–2.0 g/day)	3 weeks	RCT; AUD participants: 52 NTX 56 Acamprosate	None	(Ooteman et al., 2009) [49]
ANKK1/ DRD2	rs1800497	Bromocriptine (2.5 mg/TID)	6 weeks	RCT; AUD Australian participants: 52 Bromocriptine 31 Placebo	A1 carrier: Lower craving	(Lawford et al., 1995) [69]
	rs1800497	NTX (50 mg/day); Acamprosate (1.3–2.0 g/day)	3 weeks	RCT; AUD participants: 52 NTX 56 Acamprosate	A1 homozygotes: Greater reductions in craving on acamprosate vs NTX A2 homozygotes: Greater reductions in craving on NTX vs acamprosate	(Ooteman et al., 2009) [49]
Pharmacogenetic studies involving the glutamate system						
GRIK1	rs2832407	Topiramate (200 mg/day)	12 weeks	RCT; HD participants: 67 Topiramate 71 Placebo	CC homozygotes: Fewer heavy drinking days and greater days abstinent[a] CC homozygotes: Fewer heavy drinking days 3 and 6 months post-treatment[b]	(Kranzler et al., 2014a, Kranzler et al., 2014b) [71,72]
GRIN2B	C2664T; rs1806201	NTX (50 mg/day); Acamprosate (1.3–2.0 g/day)	3 weeks	RCT; AUD participants: 52 NTX 56 Acamprosate	None	(Ooteman et al., 2009) [49]

(*Continued*)

Table 2. (Continued).

Gene	Variant	Medication (Dosage)/	Medication Duration	Study Design/ Sample	Medication X Genetic Interaction	Reference [#]
	rs2058878; rs2300272	Acamprosate (2g/day)	12 weeks	Open-label trial; AUD participants: 110 Acamprosate	A carriers: Longer abstinence duration during first 3 months of treatment G carriers: Shorter abstinence duration during first 3 months of treatment	(Karpyak et al., 2014) [74]
Pharmacogenetic studies involving the GABA system						
GABRA6	T1519C	NTX (50 mg/day); Acamprosate (1.3–2.0 g/day)	3 weeks	RCT; AUD participants: 52 NTX 56 Acamprosate	T carriers: NTX better than acamprosate at reducing craving CC homozygotes: Acamprosate better than NTX at reducing craving	(Ooteman et al., 2009) [49]
GABRB2	C + 1412T	NTX (50 mg/day); Acamprosate (1.3–2.0 g/day)	3 weeks	RCT; AUD participants: 52 NTX 56 Acamprosate	TT or CC homozygotes: NTX reduced craving better than acamprosate	(Ooteman et al., 2009) [49]
GABRG2	G315A; rs211013	NTX (50 mg/day); Acamprosate (1.3–2.0 g/day)	3 weeks	RCT; AUD participants: 52 NTX 56 Acamprosate	None	(Ooteman et al., 2009) [49]
GABBR1	rs29220	Baclofen (30–75 mg/day)	12 weeks	RCT; AUD participants: 26 Baclofen-treated (30mg) 23 Baclofen-treated (75mg) 23 Placebo	CC homozygotes: Decreased time to relapse, DPDD, HDD, and greater % days abstinent	(Morley et al., 2018) [75]
Pharmacogenetic studies involving an alcohol metabolism gene						
ALDH2	rs671	Disulfiram (200 mg/day)	26 weeks	RCT; AUD participants: 54 Disulfiram-treated 55 Placebo	*2 carriers: Sustained abstinence vs placebo	(Yoshimura et al., 2014) [80]

OPRM1, Mu Opioid Receptor 1; *OPRK1*, Kappa Opioid Receptor 1; *OPRD1*, Delta-Opioid Receptor 1; *SLC6A4*, Serotonin Transporter; *HTR3A*, 5-Hydroxytryptamine Receptor 3A; *HTR3B*, 5-Hydroxytryptamine Receptor 3B; *DBH*, Dopamine Beta-Hydroxylase; *DRD1*, Dopamine Receptor D1; *DRD2*, Dopamine Receptor D2; *GRIK1*, Glutamate Ionotropic Receptor Kainate Type Subunit 1; *GRIN2B*, Glutamate Ionotropic Receptor NMDA Type Subunit 2B; *GABRA6*, Gamma-Aminobutyric Acid Type A Receptor Alpha6 Subunit; *GABRG2*, Gamma-Aminobutyric Acid Type A Receptor Gamma2 Subunit; *GABBR1*, Gamma-Aminobutyric Acid Type A Receptor Rho1 Subunit; *ALDH2*, Aldehyde Dehydrogenase 2 Family Member; Randomized Controlled Trial; NTX, Naltrexone; BID, Twice a Day; TID, Three Times a Day; AUD, Alcohol Use Disorder; MDD, Major Depressive Disorder; EA, Ancestry; AA, African Ancestry; H, Hispanic Ancestry.

transporter may lead to higher serotonin levels in the synapse leading to increased stimulation of postsynaptic 5-HT3 serotonin receptors, which modulate dopamine release in response to alcohol [64,65]. L homozygotes treated with sertraline reported less drinking and heavy drinking days, specifically in those individuals with a late onset of AUD. Conversely, L homozygotes with early-onset AUD reported more drinking days and heavy drinking days when treated with sertraline relative to placebo [66]. Thus, age of AUD onset combined with 5-HTTLPR genotype may predict which individuals will have better or worse clinical outcomes with SSRI treatment. Additionally, L homozygotes reported fewer drinks per drinking day and a higher percentage of days abstinent when treated with ondansetron compared to placebo, and relative to S carriers. Better clinical outcomes were seen in individuals with both the 5-HTTLPR and *SLC6A4* SNP (rs1042173). AUD individuals who possess the LL/TT genotype had the largest reductions in drinks per drinking day and increases in percentage of days abstinent when treated with ondansetron, a specific serotonin-3 (5-HT3) antagonist, relative to other genotype combinations [67].

Postsynaptic 5-HT3 receptors are ion channels wherein conduction is dependent on receptor subunits, 5-HT3A and 5-HT3B. The subunits are encoded by the *HTR3A* and *HTR3B* genes. AUD individuals treated with ondansetron and were carriers of one or more of the polymorphisms in *HTR3A* (rs11502260-AG and rs1176713-GG) and *HTR3B* (rs1761492-AC), along with polymorphisms in 5-HTTLPR and *SLC6A4* SNP (rs1042173) reported fewer drinking and heavy drinking days, as well as more days abstinent [68]. Thus, efficacy of serotonergic drugs may be enhanced in AUD individuals who possess a select combination of polymorphisms in serotonergic genes. This is currently being explored in an ongoing pharmacogenetic clinical trial of ondansetron in AUD (ClinicalTrials.gov Identifier: NCT02354703).

2.3. Pharmacogenetic studies involving catecholamines

Alcohol, like most drugs of abuse, increases dopamine release in the ventral striatum. There are five main types of dopamine receptors that are organized into two families, D1-like and D2-like, all of which are G-coupled protein

receptors. The Taq1A polymorphism, located downstream of the dopamine receptor 2 (*DRD2*) and within the Ankyrin Repeat and Kinase Domain Containing 1 (*ANKK1*) gene, has been shown to moderate treatments in individuals with AUD (see Table 2). Ooteman et al. [49] found that AUD individuals who were A1 homozygotes benefited more from acamprosate versus NTX on cue-induced craving relative to A2 homozygotes, who benefited more from NTX versus acamprosate. In another study of AUD individuals, A1 carriers treated with bromocriptine, a D2 agonist, had lower craving for alcohol relative to A2 homozygotes [69]. Additionally, dopamine can be converted to the neurotransmitter norepinephrine by the enzyme dopamine beta-hydroxylase (DBH). A SNP (rs1611115) in the *DBH* gene has been shown to moderate NTX responses in AUD individuals. Specifically, NTX-treated T carriers had more abstinence from heavy drinking than those with the CC genotype on NTX [54]. Conversely, NTX-treated C homozygotes had lower abstinence rates compared to placebo-treated C homozygotes. Taken together, genetic variants in the catecholamine system may help identify individuals with AUD who will respond better or do worse on NTX relative to placebo.

2.4. Pharmacogenetic studies involving the glutamate system

Acute alcohol intake inhibits glutamate neurotransmission by reducing glutamate binding at the NMDA receptor. Indeed, glutamatergic dysregulation has been implicated in the allostatic theory of addiction [70]. Both ionotropic and metabotropic receptors mediate the synaptic effects of glutamate. Pharmacogenetic studies have focused on variants in the subunits of glutamate receptors, namely GluK1 (encoded by *GRIK1*) and GluN2B (encoded by *GRIN2B*) (see Table 2). Kranzler and colleagues [71] found that genetic variation in *GRIK1* (rs2832407) was associated with AUD and that C homozygotes showed fewer drinking days and more days abstinent when treated with topiramate versus placebo, whereas topiramate was not effective over placebo in A carriers. Furthermore, C homozygotes continued to have fewer drinking days relative to A carriers when assessed 3- and 6-months post-treatment [72]. Ray et al. [73] examined three *GRIK1* SNPs, including rs2832407, as potential moderators of severity of topiramate side effects. Results from this study showed that C homozygotes had lower adverse side effects and lower topiramate serum levels relative to A carriers.

In addition, two SNPs in *GRIN2B* may moderate the efficacy of acamprosate. G allele carriers (resulting from rs2300272) had a shorter duration of abstinence, while A carriers (rs2058878) had a longer abstinence duration during acamprosate treatment [74]. However, a separate *GRIN2B* SNP (C2664T) did not moderate treatment responses to NTX or acamprosate [49]. Overall, these genetic variants modulate the pharmacokinetic properties, as well as the therapeutic efficacy of glutamatergic modulating medications. The genetic variant in *GRIK1* as a moderator of topiramate responses is encouraging and is further being examined in an ongoing prospective clinical trial (ClinicalTrials.gov Identifier: NCT02371889).

2.5. Pharmacogenetic studies on the GABA system

Alcohol modulates GABA activity directly at receptors and indirectly via stimulation of GABA release. The GABA system contains both ionotropic ($GABA_A$) and metabotropic receptors ($GABA_B$). Pharmacogenetic studies have focused on genes that encode subunits of the $GABA_A$ receptor, *GABRA6* and *GABRG2*, as well as a gene that encodes a subunit of the $GABA_B$ receptor, *GABBR1* (see Table 2). NTX and acamprosate-induced reductions in alcohol craving were dependent on *GABRA6* genotype (T + 1519C) [49]. Acamprosate had greater efficacy on cue-induced craving in C homozygotes, while NTX had better efficacy in A carriers. This study also examined an SNP in *GABRG2* (G + 3145A) that did not moderate NTX or acamprosate effects on cue-induced craving [49]. Variation in *GABBR1* (rs29220) moderates treatment response to baclofen, a selective $GABA_B$ receptor agonist. Specifically, C homozygotes with AUD reported greater percentages of days abstinent, less drinking days, and an extended time to relapse compared to G carriers [75]. In sum, genetic variation in GABAergic signaling may be especially relevant to the subjective experience of alcohol [76] and may be useful in predicting treatment response, including clinical response to non-pharmacological treatments, such as Twelve Step Facilitation [77,78].

2.6. Pharmacogenetic studies involving alcohol metabolism enzymes

Several candidates and genome-wide association studies implicate alcohol metabolism genes in risk for AUD. Unfortunately, few studies have examined the influence of these genes on AUD medications. For the most part, alcohol metabolism occurs in the liver wherein several enzymes oxidize alcohol. Alcohol dehydrogenase converts alcohol to acetaldehyde, a potentially toxic metabolite, which is usually rapidly converted to acetic acid by the enzyme acetaldehyde dehydrogenase. Acetaldehyde dehydrogenase (ALDH) occurs in several genetic forms with differential activity. More than one third of individuals with East Asian ancestry inherit the inactive form of *ALDH2* [79]. For these individuals, alcohol consumption increases levels of acetaldehyde, causing several negative physiological consequences, such as nausea and vomiting. Thus, inactive *ALDH2* may enhance treatment response to drugs that block acetaldehyde metabolism, such as disulfiram. Yoshimura et al. [80] found that alcohol dependent individuals (ICD-9 criteria) with the inactive *ALDH2* genotype had higher rates of abstinence from alcohol when treated with disulfiram relative to carriers treated with placebo. Prospective clinical studies with larger sample sizes are needed to examine the influence of alcohol metabolism genes.

3. Recommendations for future pharmacogenetics of AUD studies

Nearly all the pharmacogenetic clinical studies discussed above were retrospective investigations, wherein individuals were randomized without regard for genotype. Although these studies are an important contribution to the path toward personalized medicine, prospectively stratifying individuals by genotype rather than phenotype is ideal, especially in complex disorders, like AUD. This method would allow

researchers to identify whether individuals with specific genotypes present with clinically identifiable AUD phenotypes. While this approach does not require a complete understanding of the etiology of AUD [81], it does require a comprehensive phenotyping of AUD based on genetic information [82]. Thus, continuing refinement of how AUD phenotypes are defined via reverse phenotyping might also be required to improve our understanding of the genetics of AUD [83]. Reverse phenotyping uses genetic markers to identify novel phenotypes by determining phenotypic groupings that are distinguished by higher rates of shared alleles compared to what is seen in traditional diagnostic criteria [83]. Taken together, these approaches have had a crucial role in understanding the genetic architecture of other psychiatric disorders, such as bipolar disorder [84], schizophrenia [85], and developmental disorder [86].

Our understanding of the neurobiology of addiction has grown exponentially over the last few decades. Drug and alcohol addiction impact brain regions that regulate reward, stress, and executive function systems [87]. These neuroadaptations are in line with a well-established heuristic framework that conceptualizes the progression from recreational drug/alcohol use to addiction [70]. This framework consists of three addiction stages: binge/intoxication, withdrawal/negative affect, and preoccupation/anticipation stage. While the amount of genomic data is growing rapidly, it is unclear how the genetic variants identified fit into the proposed addiction cycle. To address this issue, Reilly and colleagues [14] mined existing GWAS of AUD data to generate biological hypotheses for genetic variants (largely non-significant in GWAS analyses) that may play a role within one or more stages of the addiction cycle. Interestingly, none of the GWAS-identified variants overlapped with pharmacogenetic clinical studies discussed above. However, a locus in the serotonin receptor (*HTR1A*) gene was implicated in the preoccupation/anticipation stage of the addiction cycle, wherein compulsive alcohol seeking is a predominate feature. Given that genetic variations in serotonin transporter and receptor genes moderate sertraline and ondansetron efficacy [67,68,88], the utility of these medications might be further enhanced when clinical outcomes that are reflective of the preoccupation/anticipation stage are examined. Further pharmacogenetic investigations that consider associations between genetic variants and stages of the addiction cycle are warranted.

Another promising area of research involves the mapping of genetic variation onto neurocircuitry implicated in AUD. Initial validation for this approach comes from the study of postmortem human brains, from which a whole-brain genome-wide gene expression atlas has been created [89]. These maps were used to evaluate the genetic underpinnings of resting-state functional connectivity [90], which reflects the coherence between brain regions during a task-negative, resting state [91]. Resting-state functional network strength was correlated with the expression of a set of genes linked to ion channel activity and synaptic function. As aberrant connectivity patterns are associated with several psychiatric disorders, including AUD, extending this research into populations with AUD will provide novel insights into the gene networks that are causal to AUD.

The growing popularity of personal genomics and biotechnology companies over the last decade has allowed for the use of large population-based cohorts to examine the genetic factors that contribute to alcohol problems. For example, a GWAS of the Alcohol Use Disorder Identification Test (AUDIT) was conducted using a sample of 23,328 individuals from a private genetics company (23andMe, Inc.) [92]. The AUDIT is a commonly used measure to assess hazardous patterns of alcohol consumption in the past year. Although no genetic loci reached the statistical significance threshold commonly used in GWAS studies, one of the most significant associations was in the alcohol metabolizing *ADH1C* gene (rs141973904), a finding that complements previous GWAS of AUD. In a follow-up study, a GWAS meta-analysis of AUDIT total scores was performed using the 23andMe cohort and another large population-based cohort (UK Biobank) leading to a sample of 141,932 individuals [30]. This investigation identified 10 associated risk alleles, some of which were loci that corroborated GWAS of AUD and other loci were novel associations. While these studies demonstrate the utility of large population-based cohorts, it is important to note that these research participants were not screened for clinical AUD diagnostic criteria and, thus, the identified genetic variants may better generalize to alcohol endophenotypes instead of reflecting AUD. However, large-scale biobanks such as the Million Veteran Program can link genotypes to health information documented in electronic health records. Using this approach, a recent GWAS of 274,424 ethnically diverse individuals found that genetic variants associated with alcohol consumption and AUD can be differentiated [29]. Thus, elucidating the genetic variants that contribute to AUD versus alcohol consumption using larger population-based cohorts may help identify potential targets for medication development.

4. Expert opinion

The literature on the pharmacogenetics of AUD has yielded promising results; however, there has been a lack of replication across studies and studies using prospective genotyping have yielded null results. Subsequently, the clinical utility of pharmacogenetics in AUD populations is uncertain at this time. An important consideration in pharmacogenetic research is the fact that sample sizes are limited by the scope of clinical trials; yet, GWAS-level studies of treatment response may be possible *post hoc*. Indeed, these analyses may be feasible using data from electronic health records [33,93]. For example, using propensity score models and matching, electronic health records were used to determine that gabapentin decreased AUDIT-C scores in AUD patients relative to matched unexposed patients [94]. A similar approach can be used to support a GWAS of treatment response to AUD medications. Using mechanistic studies and harvesting findings from GWAS represents an important way in which relevant AUD-genetics findings can be translated into clinical applications through precision medicine. In addition, it is encouraging that there are several ongoing prospective clinical trials on the pharmacogenetics of AUD medications, some of which are assessing the impact of combinations of

genetic variants. We recommend that future work considers reverse translating of GWAS-identified genetic variants to AUD phenotypes, mapping genes to phases of the addiction cycle, mapping genes to neural circuits, and utilizing large population-based samples. Such information will improve our understanding of the genetic architecture of AUD, leading to more effective personalized treatment strategies.

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