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## Pharmacogenetics of alcoholism treatment: Implications of ethnic diversity

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### Abstract

**Background and Objectives**—Pharmacogenetic studies of alcohol use disorder (AUD) have suggested that the efficacy of treatments for AUD is, in part, influenced by the genetic background of an individual. Since the frequency of alleles associated with pharmacotherapy for AUD varies by ancestral background, the effectiveness of medications used to treat AUD may vary among different populations. The purpose of this review is to summarize the existing pharmacogenetic studies of treatments for AUD in individuals of European, East Asian, African, and American Indian/Alaska Native ancestry.

**Methods**—Electronic databases were searched for pharmacogenetic studies of AUD treatment that included individuals of diverse ancestral backgrounds.

**Results**—Pharmacogenetic studies of AUD reviewed here have primarily investigated genetic variation thought to play a role in the response to naltrexone, ondansetron, and topiramate. There is support that the A118G polymorphism should be further investigated in individuals of East Asian ancestry.

**Discussion and Conclusions**—Given the lack of pharmacogenetic research on response to AUD medication in ethnic minority populations and the mixed results, there is a critical need for future studies among individuals of different ancestries. More efforts should be devoted to standardizing procedures such that results can be more readily integrated into a body of literature that can directly inform clinical practice.

**Scientific Significance**—This review highlights the importance for future research to aim for inclusiveness in pharmacogenetic studies of AUD and increase diversity of clinical trials in order to provide the best treatment outcomes for individuals across different racial and ethnic groups.

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## 1. Introduction

There have been an abundance of both animal and human studies highlighting the importance of genetic factors in alcohol use disorder (AUD) and how these factors, in turn, affect response to treatment (for review see<sup>1</sup>). Genetic factors are thought to account for nearly half of the vulnerabilities leading to AUD as determined using twin, adoption, and family studies.<sup>2</sup> Furthermore, ancestry significantly influences alcohol response and patterns of alcohol use.<sup>2</sup>

As AUD has a large genetic component, specific risk-conferring genes may be captured through variance in single nucleotide polymorphisms (SNPs) in candidate genes which, in turn, serve as determinants of alcohol consumption and response to alcohol as a pharmacological agent itself (for review see<sup>3</sup>). As an example, in a genome-wide association study using a sample of individuals of Asian ancestry, Quillen et al. reported that SNPs found in the aldehyde dehydrogenase (*ALDH2*) region are strongly associated with both flushing response and daily maximum drinks.<sup>4</sup> Similarly, genetic variance not only affects response to alcohol, but can affect response to pharmacotherapies. A study conducted by Kiefer et al., in a sample largely comprised of individuals of European ancestry, found that a SNP in the gene for GATA-binding protein 4 (*GATA4*), rs13273672, believed to be important in embryogenesis and regulation of myocardial differentiation and function,<sup>5, 6</sup> was associated with relapse and more importantly, with response to acamprostate.<sup>7</sup> Individuals homozygous for the G allele were more likely to relapse to heavy drinking by the end of the treatment period compared to A/A or A/G individuals. This is just one example of how certain genetic alleles influence pharmacologic response to AUD medications (recently reviewed by<sup>8</sup>).

Among individuals of non-European ancestries, certain genetic polymorphisms have been associated with both increased risk for AUD and protective effects against the development of AUD. In a study comparing alcohol dependent (AD) individuals of African ancestry and healthy controls, Ittiwut et al. identified differences in SNPs spanning Gamma-Aminobutyric Acid subtype A Receptor ( $GABA_A R$ ), Gamma 1 gene (*GABRG1*), and  $GABA_A R$ , Alpha 2 gene (*GABRA2*) and their association with alcohol dependence.<sup>9</sup> This is of particular importance as the GABAergic system is a known, primary target of alcohol and recent literature has identified GABAA receptor genes, specifically *GABRA2*, as a candidate gene for AUD.<sup>10</sup> Similarly, in this same population, a variant of the alcohol dehydrogenase 1B gene, *ADHI B\*3*, along with two variants of the aldehyde dehydrogenase 1 family member A1 gene, *ALDH1 A1\*2* and *ALDH1 A1\*3*, also appear to have protective effects against alcoholism.<sup>11</sup> Furthermore, in Southwest Indians, *ADHI B\*3* has shown protective effects against alcoholism,<sup>12</sup> while in Mexican American men, a variant of the alcohol dehydrogenase 1C gene, *ADH1C\*2*, and cytochrome P450 2E1 (*CYP2E1*) c2/C alleles are associated with alcohol dependence.<sup>13</sup> Not only does ancestral background influence risk for or protection against AUD, but it also affects response to pharmacotherapy (for review see<sup>14</sup>). Thus far, the most well studied pharmacogenetic effects have been reported for naltrexone (NTX), ondansetron, topiramate, and acamprostate,<sup>15</sup> with NTX representing the most widely studied pharmacotherapy. However, very few studies to date have considered ancestry as a moderator of pharmacogenetic response in individuals with

AUD, or have replicated findings from participants of European ancestry to ethnically diverse samples.

The present review discusses personalized treatment of AUD and considers genetic variation as a predictor of clinical response to pharmacotherapy for AUD. While we acknowledge that pharmacogenetics can also affect response to alcohol itself, the literature on genetics of alcohol response is beyond the scope of this review and is discussed elsewhere in this special issue and in previously published reports (for review see<sup>16</sup>). Specifically, we focused the present review on studies assessing the effect of gene variants on AUD treatment response among diverse ancestries. We begin with a discussion of health disparities in treatments for AUD, then review the existing studies of pharmacogenetics of treatment response in alcoholism among individuals of diverse ancestries, and conclude with recommendations for future research in this relatively new era of precision medicine.

## 2. Existing Health Disparities Among Ethnic Minority Groups

Pharmacotherapies for AUD in ethnic minority populations represent an important line of research in view of the reported disparities in the use of alcohol treatment services and the differences in alcohol consumption and consequences from alcohol use across ethnic groups (for review see<sup>17</sup>). A recent longitudinal study conducted by Mulia et al. examined disparities in the use of alcohol treatment services. The authors compared six different racial-ethnic groups (European Americans, African Americans, US born Hispanics, immigrant Hispanics, East Asian Americans and Pacific Islanders, and American Indians<sup>1</sup>) on odds of receiving an alcohol intervention during a four-year period and found that minorities (n=3,219) had significantly lower odds of receiving treatment compared to European Americans (OR=0.62). Individually, US born Hispanics (OR=0.38) and immigrant Hispanics (OR=0.13) both had significantly lower odds of receiving an alcohol intervention during the four-year period compared to European Americans. Interestingly, after adjusting for demographics and drinking-related variables, the differences between European Americans and ethnic minorities became stronger in statistical significance. Given ethnic disparities in alcohol-related problems and access to effective treatments,<sup>17</sup> consideration of ethnic background in clinical trials and human laboratory studies may provide greater access to personalized treatments for AUD that are sensitive to ethnic differences in treatment response.

Not only does it appear that racial-ethnic minorities have lower odds of receiving treatment, but these minority groups may actually benefit from additional treatment support compared to European Americans.<sup>18</sup> A study by Acevedo et al. assessed whether there were racial-ethnic disparities in the probability to seek treatment for substance use disorder.<sup>18</sup> The authors determined whether participation in outpatient treatment was correlated with subsequent arrests, treatment engagement and time to an arrest as the primary outcomes among European Americans, African Americans,<sup>2</sup> Latinos, and American Indians from four distinct geographical locations. They found significant differences in both treatment

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<sup>1</sup>American Indian individuals were referred to as “Native Americans”, while European Americans were referred to as “Whites” in this study. These terms were replaced in order to use consistent terminology and will be used throughout the manuscript when referring to these racial groups.

initiation and engagement among the racial-ethnic groups. For example, in New York, African Americans were less likely to engage in treatment compared to European Americans. Furthermore, they found that treatment engagement was related to a decrease in subsequent arrests; however, the extent of the effect varied by geographic location. Not only does this study suggest that there are disparities among treatment initiation and treatment engagement between racial and ethnic groups, but these data provide evidence of the need to personalize AUD medication across different ancestries.

### 3. Pharmacogenetic Studies of Treatment for Alcohol Use Disorder in Individuals of Diverse Ancestries

As noted above, the majority of prior pharmacogenetic studies examining the efficacy of FDA-approved and non-approved treatments for AUD have largely included participants of European ancestry (for review, see<sup>8</sup>). However, the existing health disparities in AUD treatment underscore the need to advance research in pharmacogenetic studies of treatments for AUD. Given that the frequency of alleles for many of the genes implicated in AUD differs by ancestry,<sup>19</sup> and that the subjective effects of alcohol and alcohol metabolism are influenced by genetic variation of these loci,<sup>20–22</sup> it is critical to understand how treatments for AUD interact with candidate genes across individuals of different ancestries. The following section reviews pharmacogenetic studies of AUD treatment in individuals of European, East Asian, African, and American Indian/Alaska Native ancestry (Table 1).

#### 3.1 Individuals of European Ancestry

Variations in the  $\mu$ -opioid receptor (*OPRM1*) gene and response to NTX are among the most commonly investigated pharmacogenetic effects in research on AUDs. The majority of pharmacogenetics research in AUDs has been conducted in individuals of European ancestry, and these studies have largely focused on the A118G SNP of the  $\mu$ -opioid receptor. The A118G SNP encodes the substitution of aspartic acid for asparagine (Asn40Asp) with some studies suggesting that G allele (Asp40) carriers<sup>3</sup> have a greater response to hedonic and stimulating effects of alcohol,<sup>21, 22</sup> make more requests for alcohol during self-administration, and subsequently achieve higher peak breath alcohol concentrations (BrACs).<sup>23</sup> While evidence for the association of the A118G SNP and AUD risk has been mixed,<sup>24–26</sup> a recent meta-analysis that included over 28,000 participants of European ancestry suggested that the G allele provided a moderate protective effect against the development of substance dependence,<sup>27</sup> although a different meta-analysis indicated that G allele carriers of Asian ancestry were at increased risk for developing an AUD.<sup>28</sup> Differences in the relationship between A118G allele type and AUD risk across ancestries could necessitate tailoring pharmacologic treatments to individuals who carry alleles that result in the best response to the specific treatment in question.

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<sup>2</sup>African American individuals were referred to as “Blacks” in this study. This term was replaced in order to use consistent terminology and will be used throughout the manuscript when referring to this racial group.

<sup>3</sup>G allele is synonymous with Asp40, while A allele is synonymous with Asn40, and both are used interchangeably throughout the manuscript.

Many studies have examined the A118G SNP and response to NTX in individuals with AUD who are of European ancestry.<sup>29–35</sup> For example, Oslin et al. conducted a study examining the association of A118G polymorphism and response to NTX; they found that A/G and G/G carriers had lower rates of relapse and increased time to heavy drinking over the 12-week treatment period compared to A/A carriers, suggesting that this polymorphism can be used to identify individuals who are more likely to benefit from treatment with NTX.<sup>29</sup> Similarly, data from the Combined Pharmacotherapies and Behavioral Interventions for Alcohol Dependence (COMBINE) study from individuals of European ancestry who provided DNA samples were used to determine the ability of this polymorphism to predict NTX treatment response.<sup>32</sup> Subjects with an Asp40 allele experienced more days abstinent and fewer heavy drinking days with medical management (MM) and NTX compared with medical management and placebo; there was no difference observed between treatment groups in individuals with the Asn40/Asn40 genotype. Furthermore, Asp40 carriers, compared to Asn40Asn40 carriers, had significantly better clinical outcomes when treated with NTX. Interestingly, no significant treatment-by-genotype interactions were observed when participants received MM in combination with combined behavioral intervention (CBI). The authors suggested that this may be due to CBI compensating for the placebo effect by being an intensive and effective intervention that could have precluded NTX-by-gene interactions from being observed.<sup>32</sup> While this is a plausible hypothesis, more research is needed to understand why genetic effects may be suppressed when behavioral therapy is also provided. Finally, in addition to the association between the *OPRM1* polymorphism and response to NTX, Schacht et al. reported that variation at a variable number tandem repeat (VNTR) polymorphism in the dopamine transporter gene (*DAT1/SLC6A3*) may moderate NTX and Asp40 allele effects on cue-elicited activation in the ventral striatum and the orbitofrontal cortex, highlighting the importance of these polymorphisms in reward processing.<sup>36</sup>

These results, however, are inconsistent with additional reports that found no association between the *OPRM1* Asn40Asp polymorphism and response to NTX in primarily European-American samples.<sup>31, 34</sup> In a study conducted by Gelernter et al., only males who participated in a Veterans Affairs Cooperative Study were recruited.<sup>31</sup> They found that there were no interactions between treatment response and genotype. It is possible, however, that this population is unique in regards to the frequency of comorbidities present among individuals, which may have been a confounding variable. For example, within the sample for which they received genotype data, 1.5% of the military participants had a psychiatric disability unrelated to AUD, 16.8% had a medical disability unrelated to AUD, and 15% of nonmilitary participants had either a psychiatric or medical disability unrelated to AUD. Furthermore, while the majority of this sample was comprised of European Americans (73.6%), African Americans accounted for the other 24.4%, which may have also skewed the results. Similarly, the study by Arias et al. recruited veterans who, in addition to being AD, had also been diagnosed with a mood, anxiety, or psychotic disorder.<sup>34</sup> This again could account for the discrepancy between these results and the aforementioned studies that found an association between the *OPRM1* Asn40Asp polymorphism and response to NTX in primarily European-American samples. While most previous studies have examined the interaction of NTX and the Asp40 allele in retrospective analyses of clinical trial data, a

recent prospective study of a 12-week clinical trial in which Asp40 allele carriers were oversampled, did not find any significant NTX-by-gene interactions.<sup>30</sup> This is important as the study included a large sample size of AD individuals and oversampled Asp40 carriers, yet failed to find a significant interaction. Findings showed a very small and nonsignificant effect of the Asp40 allele and in the opposite direction than predicted, namely that NTX would reduce heavy drinking in this group.<sup>30</sup> In addition to NTX, other medications have been examined to understand their influence on treatment response in Asp40 carriers. For example, a pharmacogenetic study examining the effect of nalmefene in Finnish AD individuals who carried the Asp40 allele, found no significant relationship between the G allele and treatment outcomes.<sup>37</sup> It is clear that further studies are needed to clarify the relationship between response to medications and the *OPRM1* Asn40Asp SNP as both positive and negative findings have been reported across multiple studies. Greater standardization of outcome measures across clinical trials will be needed to understand if findings from previously investigated gene-by-treatment interactions can be more consistently replicated.

In addition to the Asn40Asp polymorphism, research has been conducted on other SNPs that influence AUD medication response in individuals of European ancestry, specifically, in regards to the serotonin transporter promoter polymorphism (for review see<sup>38</sup>). These data suggest that future research should probe the association between the identified SNPs and response to selective serotonin reuptake inhibitors (SSRIs), including sertraline and fluoxetine. A study by Johnson et al. investigated the effect of variation at a VNTR in the serotonin transporter gene to examine whether it predicted treatment response to ondansetron, a 5-HT<sub>3</sub> antagonist, in participants primarily of European ancestry (n=283).<sup>39</sup> The study duration was 11 weeks and participants received cognitive behavioral therapy (CBT) plus treatment or placebo. They found that LL homozygotes of the 5-HTTLPR polymorphism of the *SLC6A4* gene had a much better response to the medication, such that drinks per drinking day were lower and percent days abstinent were higher compared to LS/SS participants. An additional benefit was seen in individuals who were TT homozygotes of the rs1042173 SNP in the same gene, such that *SLC6A4-LL/TT* individuals had the greatest proportion of abstinent days and lowest drinks/drinking day compared to individuals with other allele combinations. Within this same sample, the authors investigated the possibility of using multiple genotype combinations to better predict ondansetron treatment outcomes.<sup>40</sup> Among several polymorphisms in the 5-hydroxytryptamine receptor 3A (*HTR3A*) and receptor 3B (*HTR3B*) genes, they found possession of one of three additional genotypes, *HTR3A-rs1150226-AG*, *HTR3A-rs1176713-GG*, and/or *HTR3B-rs17614942-AC*, in combination with the genotype identified in the previously mentioned study (i.e. *SLC6A4-LL/TT*) was associated with better ondansetron treatment response.

Of importance, additional studies have been conducted in attempts to identify novel SNPs that predict response to medications in development for the treatment of AUD. Kranzler et al. have recently examined several SNPs of the Glutamate Receptor, Ionotropic, Kainate 1 (*GRIK1*) gene as predictors of response to treatment with topiramate.<sup>41</sup> While they found that topiramate, compared to placebo, was able to significantly reduce heavy drinking days and increased days abstinent in the entire sample (n=138), heavy drinking days in European Americans who participated in this study (n=122) were significantly lower, compared to

placebo, in rs2832407 C-allele homozygotes. Ray et al. also examined several SNPs of the *GRIK1* gene as predictors of topiramate-induced side effects in a sample of individuals primarily of European ancestry.<sup>42</sup> They found that the rs2832407 SNP was related to topiramate-induced side effects and the topiramate serum concentration. Specifically, this SNP in *GRIK1*, appears to moderate the effect of topiramate treatment on drinking reduction,<sup>41</sup> such that C/C homozygotes receiving topiramate significantly reduced their frequency of heavy drinking days relative to C/C homozygotes who received placebo. This effect, however, was not present in A allele carriers. A search of this SNP in the Database of Single Nucleotide Polymorphisms (dbSNP) Bethesda (MD): National Center for Biotechnology Information, National Library of Medicine,<sup>43</sup> suggests that C/C homozygotes tend to be more prevalent (35–45%) among individuals of European ancestry based on data from the HapMap project, as about 60% of individuals of European ancestry carry the C allele<sup>43,44</sup>. While additional work is needed to identify novel SNPs and establish the clinical significance of these SNPs in relation to medication development, this research highlights the importance of personalized medicine across ethnicities.

### 3.2 Individuals of East Asian Ancestry

Pharmacogenetic studies of treatment response for AUD in individuals of East Asian ancestry have largely focused on the A118G SNP and response to NTX. The allele frequencies of the A118G SNP vary as a function of ancestral background, such that individuals of East Asian ancestry are more likely to be G allele carriers relative to individuals of European ancestry, as about 40% of Koreans carry the G allele.<sup>19</sup> These differences suggest that investigation of pharmacogenetic interactions of the A118G SNP with NTX's effects is a necessary step in understanding how ancestral background influences treatment efficacy.

The first treatment trial investigating the pharmacogenetic response of NTX in a non-European sample, examined the Asn40Asp polymorphism in Korean AD individuals. This investigation found that treatment-adherent A/G or G/G (n=16) carriers took significantly longer to relapse ( $p = 0.014$ ) than A/A carriers (n=16),<sup>45</sup> similar to what has been previously reported in individuals of European ancestry, who had both significantly lower rates of relapse and a longer time to return to heavy drinking, as well as an increased percentage of days abstinent and a decreased percentage of heavy drinking days.<sup>32</sup> The underlying mechanism of this treatment response may be informed by a study of heavy drinking individuals of East Asian ancestry who were treated with NTX and received intravenous (IV) alcohol administration.<sup>46</sup> The authors found that G allele carriers (n=22) were less likely to crave alcohol when treated with NTX relative to placebo or A allele (Asn40) homozygotes (n=13;  $p < 0.05$ ). Thus, NTX appears to be most effective in Asp40 carriers, individuals who experience greater hedonic and stimulating subjective effects from alcohol administration.<sup>21, 22</sup> The findings above indicate that individuals of East Asian ancestry who carry the G allele may benefit from NTX treatment compared to Asn40 homozygotes, through a reduction of reward-related craving response, which could in turn lead to a better clinical response. A behavioral economics study of pharmacogenetic response to NTX, using the same sample of participants as the study above, implemented an Alcohol Purchase Task to understand the relative value of alcohol in heavy drinking individuals of East Asian



ancestry.<sup>47</sup> Findings suggest that relative to placebo, NTX-treated AA homozygotes had a lower intensity of demand for alcohol when consumption cost was zero ( $p = 0.07$ ). Unexpectedly, however, this effect was not present in G allele carriers treated with NTX. In order to control for potential confounders, the *ALDH2* and *ADH1B* alcohol metabolizing genes were examined as covariates in this study, but neither of these genes had any relationship with the behavioral economic measures. Thus, while in the IV alcohol administration study, NTX was effective at reducing craving in G allele carriers, findings from the behavioral economics study indicate that NTX may not be particularly effective at reducing demand for alcohol in the absence of consumption cost in individuals carrying the G risk allele. More research is needed to understand the underlying mechanisms contributing to these mixed findings.

Sex has been controlled for in some of the studies described above,<sup>47</sup> but it is important to consider that sex may also moderate the observed pharmacotherapeutic effects. A study examining the frequency of A and G alleles in AD Koreans and healthy controls indicated that the G allele was more frequent in AD women but not in AD men.<sup>48</sup> These findings suggest that the benefits of NTX treatment for Asp40 carriers may be limited to female G allele carriers. Thus, enrolling female participants in clinical trials and laboratory studies is an important step of understanding the benefits of NTX for G allele carriers of East Asian ancestry.

There is evidence that other opioid receptor antagonists, such as naloxone, moderate cortisol responses differently in Asp40 carriers relative to Asn40 homozygotes.<sup>49, 50</sup> Given the relationship between alcohol and activation of the hypothalamic-pituitary-adrenal axis,<sup>51</sup> pharmacogenetic studies of naloxone may be another important avenue of investigation in AD individuals, who show altered cortisol response.<sup>52</sup> An investigation of 30 healthy individuals (n=6 Asp40 carriers; n=24 Asn40 homozygotes) used a within-subjects design to examine the effect of naloxone or placebo on plasma cortisol and adrenocorticotropin releasing hormone levels. Healthy Asp40 carriers had higher baseline cortisol levels and higher cortisol response to IV naloxone administration than Asn40 homozygotes ( $p$ 's < 0.05),<sup>50</sup> but a subsequent study found that this effect was limited to individuals of East Asian ancestry (n=6;  $p < 0.05$ ).<sup>49</sup> These findings point to population-specific effects of opioid receptor blockade when examining Asp40 carriers and indicate that individuals of East Asian ancestry may respond differently to pharmacologic treatment, which could result in different clinical outcomes for this population.

Collectively, the studies in individuals of East Asian ancestry, to date, suggest that this population may benefit from tailored pharmacological treatments, as those who are Asp40 carriers of the *OPRM1* gene are overrepresented in individuals of East Asian relative to other ancestries. Future research may also examine the long-term benefits of NTX treatment in individuals of East Asian ancestry as well as investigate similar pharmacological treatments that have not yet been tested in this population, such as nalmefene. Furthermore, future studies should aim for larger samples as most previous research in this population has been limited to small sample sizes. The smaller sample sizes of studies in individuals of East Asian ancestry could explain why some of the promising findings with response to

NTX treatment in Asp40 carriers may not consistently replicate across larger studies that have been conducted in individuals of European ancestry.<sup>30, 34, 35</sup>

### 3.3 Individuals of African Ancestry

To date, NTX treatment response has been investigated in two pharmacologic studies among individuals of African ancestry and in one study that included predominantly African American individuals (>74%). In the latter study, twelve weeks of NTX treatment relative to placebo was associated with reductions in craving for alcohol, a decrease of subsequent drinking after consuming one drink, and a clinically significant reduction in relapse.<sup>53</sup> In contrast, a sub-analysis of the COMBINE study, which included a 16-week treatment trial with NTX, was conducted in a population of AD individuals of African ancestry, but in this sub-analysis, NTX did not have an effect on number of days abstinent, clinical outcomes, or time until the first heavy drinking day, which were the main outcomes from the COMBINE Study.<sup>54</sup> While, this study did not examine genetic moderators of treatment response, the frequency of the Asp40 allele has been shown to be <5% in individuals of African ancestry<sup>44</sup>, which could account for the poor treatment response to NTX in this study. A subsequent alcohol challenge study in social drinkers of African ancestry also did not find an effect of NTX on any subjective measures of alcohol-related effects.<sup>55</sup> However, once again, genetic moderation was not examined, nor have there been any alcohol-related challenge studies conducted in AD individuals of African ancestry. These two studies highlight both the potential lack of NTX's effect in patients of African ancestry, in addition to the unmet need for testing FDA-approved (e.g. acamprosate, disulfiram, NTX), and non-FDA approved (i.e. sertraline, topiramate) medications for the treatment of AUD in individuals of African ancestry, as NTX remains the only medication tested to date.

### 3.4 Individuals of American Indian/Alaska Native Ancestry

American Indian/Alaska Native (AI/AN) populations experience high rates of alcoholism, including the greatest lifetime prevalence of alcohol dependence, as well as the highest rates of heavy and binge drinking relative to individuals of other ancestries in the United States.<sup>56</sup> Thus, pharmacotherapeutic treatment options for reducing alcohol-related problems in individuals of AI/AN ancestry is critical. A randomized, controlled trial of 101 participants, 68 of whom were of AI/AN ancestry was conducted to examine the efficacy of NTX alone and in combination with sertraline, an SSRI, on alcohol-related outcomes after a 16-week treatment trial.<sup>57</sup> NTX treatment alone resulted in significantly lower reports of drinking-related consequences in AI/AN participants at the end of the trial (38% of sample) relative to placebo treatment (72% of sample). There was also a trend-level effect for medication treatment to increase the number of days abstinent during the trial, relative to placebo. Combination treatment with sertraline did not have a significantly different effect on alcohol use outcomes relative to NTX alone in the total sample or the subsample of AI/AN individuals. A pharmacogenetic analysis was also conducted in this study to investigate whether the presence of the Asp40 allele moderated the results. Alcohol-related treatment outcomes, such as drinking-related consequences, which were significantly reduced with NTX, did not depend on the presence of the G allele (17 of the 92 genotyped participants), as the results were nearly identical for the 75 A/A homozygotes compared to the total sample (92 genotyped participants). These findings suggest that in individuals of AI/AN

ancestry, it is possible that while NTX treatment alone is effective at reducing drinking-related consequences and increasing the number of days abstinent, The frequency of the G allele in American Indians (13%)<sup>58</sup> is similar to the frequency in individuals of European ancestry (15%)<sup>44</sup>, but much less frequent than in individuals of Asian ancestry (~40–50%)<sup>19, 44</sup>. Thus, *OPRM1* genotype may not be influencing the efficacy of NTX in individuals of AI/AN ancestry. While these findings need to be confirmed with additional clinical trials that include individuals of AI/AN ancestry, and larger sample sizes, NTX treatment may be a promising pharmacologic treatment to pursue in individuals of AI/AN ancestry who suffer disproportionately from lifetime alcohol dependence and heavy drinking relative to individuals of other ancestries in the United States.<sup>56</sup>

#### 4. Discussion

It is well-established that given the heterogeneity and complexity of AUD, as well as differences in consumption and consequences of alcohol use among ethnic groups (for review see<sup>17</sup>), there is an unmet need for personalized AUD treatment.<sup>59</sup> Given the rather modest clinical effects associated with the currently approved medications for AUD, not only is it necessary to develop novel therapeutics for the treatment of AUD, but it is also important to identify those patients most likely to respond to the available medications to improve treatment outcomes.<sup>60</sup> This review summarizes existing studies that analyze the effect of gene variants on AUD pharmacotherapy response in individuals of diverse ancestries. We first highlighted the implications of health disparities in access to healthcare and response to treatment. Then, we reviewed the current literature discussing AUD treatment response among individuals of different ancestries and the role of pharmacogenetics in treatment response. The most frequently studied polymorphism is the Asn40Asp SNP of the *OPRM1* gene. While the findings are mixed for individuals of European ancestry, more promising findings emerge among G allele carriers of East Asian ancestry.<sup>45,46</sup> This population may benefit the most from NTX treatment relative to individuals of other ancestries, but further studies are needed with much larger sample sizes to replicate these effects. However, very few studies exist on pharmacogenetics of AUD in individuals of African or AI/AN ancestry, so the field is far from being able to make any conclusions in these populations, and we found no pharmacogenetic studies of AUD in individuals of predominantly Hispanic and/or Latino ancestry. Thus, there is significant work to be done to understand which populations respond most favorably to a medication, with the hope that these advances in pharmacogenetics and precision medicine will decrease exposure to treatments that are known to be ineffective in certain individuals.

It is also important to note that while a heterogeneous sample may be more generalizable, it is not the most effective or informative measure of treatment effects given the known association of genetic markers and other variables including sex and cortisol levels. Rather, the need for carefully designed prospective clinical trials targeted to the population that will generate the best response to the experimental treatment in an effort to increase the probability of detecting an effect and to maximize treatment outcomes is critical.<sup>60, 61</sup> Oftentimes, there are no standardized methods across AUD clinical trials making it difficult to compare studies, which may be, in part, responsible for the numerous discrepancies in the aforementioned studies.<sup>62</sup> While the authors acknowledge the clinical application of this

research is limited, given the known effect of genetics on response to medication, the use of genotype testing to predict response to AUD medication is a promising approach and requires additional research with standardized methods and stronger reproducible findings. The trend towards standardizing procedures is also noted in the clinical trials arena wherein new medications may be developed and ultimately receive FDA approval for the indication of AUD.<sup>63, 64</sup>

As elegantly discussed by Tate and Goldstein, health disparities among individuals of different ancestries can be reduced by making medicines more inclusive.<sup>65</sup> This should be achieved by conducting pharmacogenetics research in populations of diverse ancestral background and by increasing the diversity of clinical trial enrollment. Further, it is important to consider ancestral and genetic background of the individual as it remains unclear what factors are primarily contributing to drug response whether it be genetics, environmental correlates of drug response within a specific population, or their interaction.<sup>65</sup> Additionally, laboratory experimental psychopathology studies that examine genetic moderators of pharmacotherapeutic response during alcohol administration, behavioral economics, alcohol cue, and stress reactivity paradigms are largely absent in ethnic minority populations, with a few exceptions.<sup>47, 49</sup> Conducting these studies would advance research aimed at understanding the mechanisms by which specific genetic alleles moderate the response to pharmacotherapies for AUD, which could in turn inform clinical trials of AUD treatments among different racial and ethnic populations. These goals for inclusive healthcare should be addressed in pharmacogenetics research and clinical trials of individuals with AUD.

The advancement of pharmacogenetics and personalized medicine provides promise for more effective treatments across populations, but it is essential to discuss the care that should be taken for integrating pharmacogenetics into clinical practice. There is considerable controversy on the use of race in research and how to best translate results from studies that have used racial categories<sup>66, 67</sup>. There is the possibility of misusing terms associated with race and/or genetic variation that can result in negative social consequences<sup>66, 67</sup>. Interviews with clinicians suggest that individually tailored treatment based on pharmacogenetics information is still in its infancy and that currently, racial identity is used to represent someone's genetic ancestry<sup>68</sup>. Thus, continued discussions on the ethics of pharmacogenetics research need to be encouraged to best inform the use of genetic ancestry information in clinical practice.

While this review focuses on pharmacogenetic studies of treatment for AUD in four different ancestries including European, East Asian, African American, and American Indian/Alaskan Native, it is important to acknowledge that there is much variation in regards to genetics, culture and environmental exposure within each broader classification.<sup>69</sup> Another limitation of many pharmacogenetic studies is that participants are often asked to self-identify as a specific ethnicity. Due to recent genetic admixture, it is becoming increasingly difficult to rely on self-reports for pharmacogenetic studies. Therefore, the use of ancestry-informative markers is encouraged to accurately detect stratification in the aforementioned admixed populations such as Latinos and Hispanics.

In conclusion, this review highlights the lack of experimental psychopathology laboratory studies among individuals of non-European ancestry with AUD and the near absence of subjects of non-European ancestry in clinical trials examining pharmacologic treatments for AUD. We emphasize the need for pharmacogenetic studies that address the role of ethnic diversity to contribute to inclusive healthcare and personalized medicine for the treatment of AUD.

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**Table 1**  
Pharmacogenetic Studies in the Treatment of Alcohol Use Disorder among Diverse Ancestries

Primary Ancestry	Study	Gene	Polymorphism	Alleles	Allele Frequencies Across Populations	Medication	Sample Size (N)	Gene-by-Medication Findings
European	Oslin et al., 2003	<i>OPRM1</i>	rs1799971	A/G	CEU (0.85/0.15), JPT (0.51/0.49), ASW (0.95/0.05)	NTX	141	↑ G allele carriers
	Gelemler et al., 2007 <sup>b</sup>	<i>OPRM1</i>	rs1799971			NTX	215	↔
	Anton et al., 2008	<i>OPRM1</i>	rs1799971			NTX	604	↑ G allele carriers
	Ooiteman et al., 2009 <sup>b</sup>	<i>OPRM1</i>	rs1799971			NTX	108	↔
	Kranzler et al., 2013	<i>OPRM1</i>	rs1799971			NTX	158	↑ G allele carriers
	Arias et al., 2014 <sup>b</sup>	<i>OPRM1</i>	rs1799971			NTX	107	↔
	Oslin et al., 2015	<i>OPRM1</i>	rs1799971			NTX	221	↔
	Arias et al., 2008 <sup>b</sup>	<i>OPRM1</i>	rs1799971			Nalmefene	272	↔
	Johnson et al., 2011	<i>SLC6A4</i>	5-HTTLPR <sup>d</sup> + rs1042173	A/C	CEU (0.58/0.42), JPT (0.16/0.84), ASW (0.77/0.23)	Ondansetron	283	↑ LL homozygotes ↑ LL/TT homozygotes
	Johnson et al., 2013	<i>SLC6A4</i> , <i>HTR3A</i> , <i>HTR3B</i>	5-HTTLPR + rs1042173 <i>HTR3A</i> -rs1150226 <i>HTR3A</i> -rs1176713	A/G A/G A/C	CEU (0.05/0.95), JPT (0/1),	Ondansetron	283	↑ <i>HTR3A</i> -rs1150226-AG, <i>HTR3A</i> -rs1176713-GG, and/or

Primary Ancestry	Study	Gene	Polymorphism	Alleles	Allele Frequencies Across Populations	Medication	Sample Size (N)	Gene-by-Medication Findings
			<i>HTR3B-rs17614942</i>		ASW (0.31/0.69) CEU (0.76/0.24), JPT (0.77/0.23), ASW (0.69/0.31) CEU (0.05/0/0.95), JPT (0/1), ASW (0.11/0.89)			<i>HTR3B-rs17614942-AC + SLC6A4-LL/TT</i> homozygotes
	Ray et al., 2009	<i>GRIK1</i>	rs2832407	A/C	CEU (0.39/0.61), JPT (0.69/0.31), ASW (0.79/0.21)	Topiramate	51	↑ side effects in A allele carriers
	Kranzler et al., 2014	<i>GRIK1</i>	rs2832407			Topiramate	138 (122 European)	↑ C allele homozygotes
Asian/East Asian	Kim et al., 2009	<i>OPRM1</i>	rs1799971			NTX	32	↑ G allele carriers
	Ray et al., 2012	<i>OPRM1</i>	rs1799971			NTX	35	↓ craving in G allele carriers
	Bujarski et al., 2012	<i>OPRM1</i>	rs1799971			NTX	35	↓ intensity of alcohol demand in AA homozygotes
African <sup>d</sup>	Volpicelli et al., 1992	None	None			NTX	70 (55 African ancestry)	↓ craving, drinking, relapse
	Ray & Oslin, 2009	None	None			NTX	100	↔
	Plehani et al., 2011	None	None			NTX	43	↔ on subjective measures of alcohol response

Primary Ancestry	Study	Gene	Polymorphism	Alleles	Allele Frequencies Across Populations	Medication	Sample Size (N)	Gene-by-Medication Findings
AI/AN	O'Malley et al., 2008	<i>OPRM1</i>	rs1799971 <sup>e</sup>			NTX, Sertraline	101 (68 AI/AN)	↔

<sup>a</sup>While no gene-by-medication interactions have been investigated in individuals who are primary of African ancestry, studies have investigated response to treatment. Thus, for this population treatment outcomes are listed in the gene-by-medication findings column.

<sup>b</sup>Other genes examined, not discussed here.

<sup>c</sup>Populations selected from the 1000 Genomes Project (Auton, et al., 2015) as examples of different ancestries for reference, and are not meant to be inclusive of all ancestries; CEU = Utah residents with North and Western European ancestry; JPT = Japanese in Tokyo, Japan; ASW = Americans of African ancestry in SW USA.

<sup>d</sup>Extensive information on triallelic frequency for 5-HTTLPR across populations can be found in Haberstick, et al. (2015).

<sup>e</sup>Minor allele frequency for G allele in American Indian sample = 0.13 (Ehlers, Lind, & Wilhelmsen, 2008).

<sup>f</sup> = greater effect or better response to treatment in group indicated; ↔ = no gene-by-medication interaction or medication effect; ↓ = reductions in outcomes indicated; AI/AN = American Indian/Alaska Native, NTX = naltrexone