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The Pharmacogenetics of Alcohol Use Disorder

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Abstract

Background—Annually, the use and abuse of alcohol contributes to millions of deaths and billions of dollars in societ al costs. To determine the impact of genetic variation on the susceptibility to the disorder and its response to treatment, studies have been conducted to assess the contribution of a variety of candidate genetic variants. These variants, which we review here, were chosen based upon their observed or hypothesized functional relevance to AUD risk or to the mechanism by which medications used to treat the disorder exert their effects.

Methods—This qualitative review examines studies in which candidate polymorphisms were tested as moderator variables to identify pharmacogenetic effects on either the subjective response to alcohol or the outcomes of pharmacotherapy.

Results—Although findings from these studies provide evidence of a number of clinically relevant pharmacogenetic effects, the literature is limited and there are conflicting findings that require resolution.

Conclusions—Pharmacogenetic studies of AUD treatment that use greater methodological rigor and better statistical controls, such as corrections for multiple testing, may help to resolve inconsistent findings. These procedures could also lead to the discovery of more robust and clinically meaningful moderator effects. As the field evolves through methodological standardization and the use of larger study samples, pharmacogenetic research has the potential to inform clinical care by enhancing therapeutic effects and personalizing treatments. These efforts may also provide insights into the mechanisms by which medications reduce heavy drinking or promote abstinence in patients with an AUD.

Genetic Contributions to Alcohol Use and Abuse

In the development of alcohol use disorder (AUD), experimentation with alcohol may precede increased drinking frequency and intensity, which are associated with the emergence of AUD signs and symptoms. The susceptibility to AUD and its developmental course and response to treatment vary considerably among individuals. One aspect of the susceptibility to the disorder is reflected in the subjective response to alcohol, which like all

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drugs of abuse, has been shown to be partly heritable (Edwards et al., 2011; Heat et al., 1994; 2001; Kendler et al., 1992; 1999; 2000; Prescott and Kendler, 1995; Tsuang et al., 2001; van den Bree et al., 1998; Verweij et al., 2010). The application of genetic methods to the study of AUD thus has the potential to enhance our understanding of the mechanisms underlying key aspects of the development of AUD, e.g., by helping to elucidate the role of genetic variation in both the subjective effects of alcohol and the response to the pharmacological treatment of AUD. Together, these advances could inform the individualized assessment and treatment of the disorder (Kranzler and McKay, 2012).

Alcohol is the most commonly used addictive substance in the world, with the harmful use of alcohol resulting in 3.3 million deaths annually (WHO, 2014). In the United States, during a one-year period, over 17 million people (1 in 12 adults) suffer from alcohol abuse or dependence (Grant et al., 2004). Millions more people engage in risky drinking patterns that have health, social, and legal consequences (Substance Abuse and Mental Health Services Administration, 2013). The heritability (i.e., the sum of additive genetic risk) of alcohol dependence is estimated to be 50-60% (Heath et al., 1997; Kendler et al., 2007; Prescott and Kendler, 1999; Sullivan et al,, 2012). Nonetheless, research has yet to explain why some individuals are able to maintain healthy, moderate patterns of alcohol use, while others drink heavily (episodically or regularly) and experience the signs and symptoms of an AUD.

Because AUD is a prevalent public health issue, a variety of approaches have been developed to treat the disorder. This includes a growing body of literature on the development and evaluation of medications to treat AUD (Hasin et al., 2007). Three medications are currently approved by the U.S Food and Drug Administration to treat alcohol dependence: disulfiram, naltrexone, and acamprosate (see Zindel and Kranzler, 2014 for a review). Disulfiram (Antabuse) inhibits the metabolism of acet aldehyde (a toxic metabolite of alcohol) and has been used since the 1940s as an aversive agent to treat alcoholism (Hald et al., 1948). Disulfiram discourages drinking by causing unpleasant effects (e.g., headache, nausea, vomiting, chest pain, weakness, blurred vision, mental confusion, sweating, choking, breathing difficulty, and anxiety) when alcohol is consumed (Doering et al., 1999; Wright and Moore, 1990). Naltrexone, an opioid receptor antagonist, appears to reduce the reinforcing effects of alcohol, feelings of intoxication, and craving through blockade of the μ-opioid receptor (Rösner et al., 2010a; Williams et al., 2005). Acamprosate (Campral), a medication approved in the United States to treat alcohol dependence based on evidence of efficacy from European trials, appears to alter N-methyl-D-aspartate (NMDA) receptor composition and may have indirect effects on γ-aminobutyric acid type A ($GABA_A$) receptors (Kalk and Lingford-Hughes, 2014), reducing relapse risk (Rösner et al., 2014b).

Although placebo-controlled trials have shown both naltrexone and acamprosate to be efficacious in the treatment of AUD, systematic reviews of treatment outcomes show that 38-70% of subjects treated with one or the other of these medications do not respond to the treatment (Mason et al., 2001; Rösner et al., 2010a; Srisurapanont and Jarusuraisin, 2005). Due to the limited efficacy and variable treatment response for the approved medications, there are increasing efforts to identify new medications using study designs that also test

whether genetic variation moderates the medications' efficacy (Graham et al., 2002; Williams, 2005). The advantage of this approach is that it can help to define the individuals and circumstances under which the treatments exert their greatest beneficial effects and potentially provide insight into the mechanisms by which the medications produce their therapeutic and adverse effects.

In this qualitative review, we summarize the clinical pharmacogenetic findings for AUD, focusing both on genetic moderation of the subjective effects of alcohol, which influence an individual's susceptibility to abuse alcohol, and the response to pharmacological treatments to reduce heavy drinking or promote abstinence. Using PubMed and PsychINFO, we searched for English-language articles published between 1970 and 2014. We included various combinations of the following search terms: genetics, polymorphism, SNP, pharmacogenetics, alcohol, alcohol abuse, and alcohol use disorder. Using this method, we identified over 200 publications. After removing duplicates, we reviewed the titles and/or abstracts to ensure relevance; Data from approximately 80 articles are included here. The number of available studies using similar methods and outcomes is limited, so the present review is qualitative, rather than being meta-analytic. The information taken from these pharmacogenetic studies has potentially far-reaching implications, as it may enable the use of genetic testing both to identify individuals at risk to develop an AUD and to use genotype(s) to select pharmacological treatments to improve outcomes for individual patients.

Pharmacogenetics of Subjective Effects Associated with Alcohol Use

One of the goals of alcohol pharmacogenetics research is to identify which individuals are at increased risk to develop an AUD. One approach to answering this important question involves studying the impact of genetic variation on the subjective responses to alcohol. Subjective, reinforcing effects of alcohol are thought to contribute to its abuse potential. Laboratory studies have shown that the balance of rewarding and aversive effects produced by drug administration is strongly predictive of abuse in the natural setting (Bauer and Hesselbrock 1993; Comer et al., 2010; Foltin and Fischman, 1991). A growing number of human alcohol challenge studies have examined the moderating effects of genetic variants, chosen for their hypothesized or demonstrated functional effects, on the subjective responses to alcohol.

Although the focus of this review is on the genetic moderation of pharmacodynamic effects of alcohol and alcohol treatment, it is important to recognize that robust examples of genetic variation influencing alcohol's subjective effects and abuse liability are seen with genes that encode the enzymes primarily responsible for the metabolism of alcohol: the alcohol dehydrogenases (ADHs) and aldehyde dehydrogenases (ALDHs) (Agarwal and Goedde, 1992). There are multiple isozymes of ADH and ALDH that are encoded by different genes, resulting in protein products that differ significantly in their metabolic activity (Crabb et al., 2004). Some ADH gene variants encode enzymes with higher metabolic activity, resulting in the accumulation of acet aldehyde, which can produce facial flushing, nausea, rapid heartbeat, and other aversive effects. Similarly, a null allele in *ALDH2* causes an accumulation of acet aldehyde by preventing its catabolism to acetate (Harada et al. 1981).

These effects have mostly been identified in East Asians, where homozygosity of an *ADH1B* variant can reduce the risk of alcohol dependence by eight-fold in East Asians (Peng and Yin, 2009). Further, in these populations, homozygosity of *ALDH2* is highly protective against the disorder (Peng and Yin, 2009). There is growing evidence that *ADH1B* variants have similar protective effects against alcohol dependence in both European and African ancestry populations as well (Gelernter et al., 2014).

Despite a substantial literature showing protective effects of variation in the alcohol metabolism genes on risk of alcohol dependence, there is little evidence regarding these variants moderating medication response. One recent exception involves disulfiram, a pharmacologic antagonist of ALDH2, the effects of which mimick those of the null *ALDH2* allele. Yoshimura et al. (2014) found that, in a small subsample of individuals treated with disulfiram, the presence of the *ALDH2* variant was associated with a higher rate of abstinence from alcohol. A moderator effect of the *ALDH2* variant variant has also been demonstrated in a human alcohol challenge study (Peng et al., 2014).

Opioidergic Genes

Other potential genetic moderator of the response to alcohol maps to exon 1 of the μ-opioid receptor gene (*OPRM1*). A single nucleotide polymorphism (SNP) (A118G, rs1799971) alters the receptor's amino acid sequence by substituting aspartic acid for asparagine (Asn40Asp40). In some studies, this SNP has been associated with an increased susceptibility to alcohol dependence (Bart et al., 2005; Town et al., 1999). However, a meta-analysis, found no effect of the SNP on risk of alcohol or other substance dependence (Arias et al., 2006).

Ray et al. (2013) studied alcohol-dependent individuals who completed test sessions in which their subjective responses to intravenous infusions of alcohol (target breath alcohol concentration (BrAC) = 0.06 g/dL) were measured. They found that G-allele carriers (n = 20) reported significantly greater alcohol-induced stimulation, vigor, and positive mood than A-allele homozygotes (n=23). This study replicated the results of two previous studies by these investigators in which G-allele carriers reported greater sensitivity to the stimulant and hedonic effects of alcohol (Ray and Hutchison, 2004, Ray et al., 2010). Although a recent investigation failed to show that the A118G SNP moderated the subjective response to intravenous alcohol, when G-allele carriers were allowed to self-administer alcohol, they made significantly more alcohol requests than A-allele homozygotes, achieving a significantly higher peak BrAC (Hendershot et al., 2014).

Dopaminergic Genes

Variation in dopaminergic genes may also moderate the hedonic effects of alcohol. The dopamine transporter (DAT) protein, encoded by *SLC6A3*, regulates the removal of dopamine (DA) from the synaptic cleft. *SLC6A3* contains a 40-base-pair variable number of tandem repeats (VNTR) polymorphism (rs28363170), the most common alleles of which are the 9 (A9) and 10 (A10) repeat alleles. Because the A10 is associated with higher DAT expression and greater DA clearance, A9 carriers are thought to have higher synaptic dopamine levels than A10 homozygotes (Fuke et al., 2001). The A9 allele has been

associated with severe alcohol dependence (Du et al., 2011; Köhnke et al., 2005; Sander et al., 1997b). In a re-analysis of data from an intravenous alcohol challenge study, Ray and colleagues (2014) found that *OPRM1* G-allele carriers who were also *SLC6A3* A10 homozygotes reported steeper increases in the effects of alcohol dosage on stimulation and positive mood than were seen in the other genotype groups.

Variation in GABAergic, Neurosteroidergic, and Serotonergic Genes

Gamma-aminobutyric acid, type A ($GABA_A$) receptors have been shown to mediate several behavioral effects of alcohol (e.g., Davies, 2003; Grobin et al., 1998; Hanchar et al., 2005), making them the focus of a number of candidate-gene studies for alcohol dependence. The most consistent findings for association of $GABA_A$ genes with alcohol dependence is with SNPs in the gene encoding the α2 subunit (*GABRA2*) (Edenberg et al., 2004; see Li et al., 2014 for a meta-analysis).

A synonymous A-to-G substitution in exon 4 of *GABRA2* (rs279858) has also been associated with differences in the subjective effects of oral alcohol. Arias and colleagues (2014a) found greater stimulatory and euphoric effects of alcohol (target BrAC of 40 mg% (0.04%) and 100 mg% (0.10%)) in carriers of the rs279858 C allele among a sample of 52 “light” and “heavy” drinkers. The direction of the genotype by drug interaction reported by Arias contrasted with those of previous reports. In an earlier study of 27 healthy individuals, those homozygous for the major A-allele of rs279858 reported greater overall subjective alcohol effects (including stimulant and sedative effects) than the other genotype groups (Pierucci-Lagha et al., 2005). Similarly, in a study of 69 healthy individuals, carriers of the minor allele of *GABRA2* SNPs rs279858, rs279844, rs279845, rs279826, rs279828 and rs279836 reported fewer aversive effects of orally administered alcohol, which yielded a mean peak BrAC of 100.4 mg/dL (Uhart et al., 2013). In a challenge study conducted in 110 Japanese subjects (Roh et al., 2011), those with one or two copies of the major alleles of the *GABRA2* SNPs rs279869, rs279858, and rs279837 reported greater subjective responses to intravenous alcohol (target BrAC = 50 mg/dL).

Based on rodent and *in vitro* studies that implicate endogenous neuroactive steroids as mediators of alcohol's effects at $GABA_A$ receptors, Milivojevic et al. (2011) examined the association between alcohol dependence and variation in *SRD5A1*, which encodes 5α-reductase, and *AKR1C3*, which encodes 3α-hydroxysteroid dehydrogenase, two key enzymes in the synthesis of the neuroactive steroids (Morrow et al., 2001). They found that a synonymous exon 1 SNP (rs248793) in *SRD5A1* and a non-synonymous substitution (C to G, His5Gln, rs12529) in *AKR1C3*. They found main protective effects of both minor alleles and an interaction effect on risk of alcohol dependence. Subsequently, this group showed that *AKR1C3*2* G-allele carriers demonstrated greater increases in the stimulant and sedative effects of orally administered alcohol (0.8 g/kg) than C-allele homozygotes (Milivojevic et al., 2014).

Though less well studied, there are also data to suggest that genetic variation is associated with the severity of alcohol craving. Following tryptophan depletion, alcohol-dependent participants (n = 23) underwent an alcohol cue-exposure procedure, after which subjective reports of craving were measured (Ait-Daoud et al., 2012). The study showed that a

functional SNP (T to G, rs1042173) in the gene encoding the serotonin transporter (*SLC6A4)*, which regulates the level of serotonin in the synaptic cleft, was associated with a greater urge to drink and craving for alcohol.

Genetic variation may also moderate other effects relevant to alcohol dependence, such as the severity of alcohol withdrawal. Alcohol withdrawal severity can vary from mild symptoms, such as sleep disturbances and anxiety, to severe and life threatening symptoms, including delirium, visual hallucinations, seizures and convulsions (Bayard et al., 2004). One of the variants that has been studied in relation to severe alcohol withdrawal is the 5-HTTLPR polymorphism of *SLC6A4*, which yields long (L) and short (S) alleles (Lesch et at., 1997) that differ functionally: the L allele is associated with higher levels of transcription than the S allele. Sander et al. (1997a) reported that the S allele was associated with risk of alcohol-related delirium and seizures. Karpyak et al. (2010) investigated the effects of 12 previously reported candidate gene variants in groups of alcohol-dependent participants either with (n = 112) or without (n = 92) a history of alcohol-induced seizures or delirium. Although none of the polymorphisms were significantly associated with alcohol-induced seizures or delirium after correction for multiple testing, these investigators found a significant interaction between 5-HTTLPR and a *DRD2* exon 8 SNP (*DRD2* E8, rs6276), the significance of which increased after adjustment for lifetime maximum number of drinks consumed per 24 hours. The interaction effect on delirium tremens remained significant after Bonferroni correction. They reported a decreased likelihood of delirium tremens in individuals with both the *DRD2* G allele and the *SLC6A4* LL genotype. This study is the first to implicate the interaction of serotonin and dopamine system genes in the etiology of severe alcohol withdrawal. The E8 SNP maps 52 base pairs downstream of the stop codon in the 3′ untranslated region of *DRD2* and the A/A genotype at this locus was previously associated with increased daily alcohol intake and reduced D2 function (Finckh et al. 1997; Lucht et al., 2001; Rommelspacher et al., 2001). A more recent study showed that haplotypes composed of *DRD2* and *ANKK1* polymorphisms may directly predispose alcohol-dependent patients to experience withdrawal with complications such as delirium and seizures (Kucharska-Mazur et al. 2012).

Pharmacogenetics of Treatment of Alcoholism and Alcohol Use Disorder

Research is also beginning to elucidate how genetic variation may account for the variability in response to medications used to treat AUD. In an effort to control the study conditions and thereby to reduce the error variance inherent in clinical trials, much of this work has been done in human laboratory settings, where the ability of medications to alter specific effects of alcohol is examined. The moderating effects of candidate gene variants have also been examined in clinical trials assessing the therapeutic effects of the medications to treat AUD (Table 1).

Opioidergic Genes

The majority of studies of the pharmacogenetics of alcohol treatment have focused on the moderating effects of variation in *OPRM1* on the response to the opioid antagonist naltrexone. Oslin et al. (2003) first reported that the Asp40 allele of Asn40Asp, encoded by an A118G SNP, predicted a significantly lower rate of relapse to heavy drinking in

naltrexone-treated patients than those receiving placebo. The study sample in this secondary analysis was comprised of 141 European-American individuals from three placebo-controlled treatment trials for alcohol dependence. The investigators found that Asp40-allele carriers treated with naltrexone had a significantly lower likelihood of relapse to heavy drinking than naltrexone-treated Asn40-allele homozygotes. The placebo groups did not differ as a function of genotype.

In subsequent studies, the most robust moderating effect of Asn40Asp SNP on the response to treatment with naltrexone was in a secondary analysis of the COMBINE Trial (Anton et al. 2006). In a sample of 604 alcoholics, Anton et al. (2008) found that Asp40-allele carriers treated with naltrexone (100 mg/day) reported a greater percentage of abstinent days and a lower percentage of heavy drinking days than Asn40-allele homozygotes treated with naltrexone or either placebo group. In an uncontrolled naltrexone trial (50 mg/day), Kim et al. (2009) found that alcohol-dependent individuals with one or two copies of the Asp40 allele maintained abstinence longer than Asn40-allele homozygotes, whose risk of relapse was 10.6 times that of the Asp40-allele carrier group. Despite the large difference, the effect was not statistically significant in the small sample studied (n = 66). Consistent with the moderating effects of the SNP, Chen and colleagues (2013) reported that, among 112 heavy drinkers, G-allele (Asp40-allele) carriers treated with 100 mg/day of naltrexone reported a significantly greater percentage of non-hazardous drinking days than those treated with placebo or A-allele homozygotes in either treatment group. Also consistent with a genotype × treatment interaction, using a within-day analysis, Kranzler and colleagues (2013) found, in a study of 158 heavy drinkers, that naltrexone (50 mg/day) was more effective than placebo at reducing nighttime drinking on days when individuals reported greater than average desire to drink in the evening, an association that was limited to Asp40-allele carriers.

Several polymorphisms of the delta and kappa opioid receptor genes (*OPRD1*, and *OPRK1*, respectively) may also contribute to naltrexone's pharmacological effects. Ashenhurst et al. (2012) exposed heavy drinkers (n = 40) to an intravenous alcohol challenge (target BrACs: 0.02, 0.04, and 0.06 g/dL) after three days of treatment with either placebo or naltrexone (50 mg/day). These investigators found a significant genotype × treatment interaction: in the naltrexone group, *OPRK1* SNP rs997917 T-allele homozygotes reported less alcohol-induced sedation than C-allele carriers. In addition, carriers of the A allele of the *OPRD1* SNP rs4654327 reported greater naltrexone-induced blunting of alcohol stimulation and alcohol craving than G-allele homozygotes.

In a human laboratory study in which subjects of Asian ancestry (n = 35) rated their desire to drink after receiving intravenous alcohol (target BrACs = 0.02, 0.04, and 0.06 g/dL), carriers of the Asp40 allele reported lower levels of alcohol craving following treatment with naltrexone (50 mg/day) compared to placebo (Ray et al., 2012, see also Bujarski et al, 2012). In another pharmacogenetic challenge study (Setiawan et al., 2011), 40 social drinkers were administered their preferred alcoholic beverage (males: 12 g ethanol; females: 10.4 g ethanol) following six days of pretreatment with naltrexone (50 mg/day) or placebo. Although naltrexone treatment had no impact on the reinforcing properties of alcohol,

Asp40-allele carriers reported reduced alcohol-induced euphoria following naltrexone treatment.

In contrast to these studies, a secondary analysis (Gelernter et al. 2007) of data from a subgroup of participants in the VA Cooperative Study of naltrexone to treat alcohol dependence (Krystal et al., 2001) showed that polymorphisms in *OPRM1 OPRD1*, or *OPRK1* failed to moderate the effects of naltrexone (50 mg/day). A cue- exposure trial in 93 heavy drinkers (McGeary et al., 2006) showed an association of the Asp40 SNP with the effects of naltrexone that was opposite that seen in prior studies. In that study, naltrexone (50 mg/day for 10 days) increased the urge for alcohol in Asp40-allele carriers, with no effect on this measure in Asn40 homozygotes.

Despite the variable findings concerning the moderating effect of the Asn40Asp SNP on the efficacy of naltrexone, a meta-analysis of the association concluded that alcohol dependent Asp40-allele carriers are approximately half as likely to relapse when treated with naltrexone compared with placebo (Chamorro et al., 2012). However, recently, Oslin et al. (2014), reported on the first prospective study of the Asn40Asp SNP as a moderator of naltrexone's effects in 221 alcohol-dependent individuals. These investigators found no main effect of either naltrexone or of the Asn40Asp SNP. They also found that these factors did not exert an interactive effect on the risk of relapse to heavy drinking, which was the primary outcome measure, or on any secondary outcomes.

Arias and colleagues (2008) evaluated the moderating effects of a number of *OPRM1*, *OPRD1*, and *OPRK1* polymorphisms, including rs1799971, on the response to treatment of alcohol dependence with nalmefene 20 mg/day, a mu-opioid receptor antagonist and kappa partial agonist that is approved for this indication in the European Union. This was a secondary analysis of a clinical trial that showed nalmefene to reduce significantly the number of heavy and very heavy drinking days per week relative to placebo (Karhuvaara et al., 2007). In the pharmacogenetic analysis, conducted in 272 individuals, Arias et al. (2008) found no evidence that any of the polymorphisms examined moderated the response to nalmefene treatment.

Dopaminergic Gene

Schacht and colleagues (2013), using alcohol cue-elicited brain activation, examined whether the Asn40Asp SNP and a VNTR polymorphism in *SLC6A3*, which encodes the dopamine transporter protein, moderate the effects of naltrexone treatment (50 mg/day for 7 days) in 74 non-treatment-seeking, alcohol-dependent individuals. Asp40-allele carriers treated with naltrexone showed less activation than Asn40-allele homozygotes. These same individuals, if homozygous for the 10-repeat-allele in *SLC6A3*, showed less activation than 9-repeat-allele carriers.

Another dopaminergic gene that has been examined as a moderator of the pharmacologic treatment of alcohol dependence is *DBH*, which encodes dopamine-beta-hydroxylase, which catalyzes the synthesis of norepinephrine from dopamine. In response to disulfiram treatment for cocaine dependence, individuals homozygous for the C-allele of the *DBH* C-1021T polymorphism (rs1611115) had fewer cocaine-positive urine tests than T-allele

carriers (Kosten et al., 2013). Based on this finding, Arias et al. (2014b) examined the moderating effects of the Asn40Asp SNP in *OPRM1* and the *DBH* polymorphism C-1021T in 107 alcohol-dependent individuals with co-occurring Axis I psychiatric disorders who were treated with placebo alone, naltrexone alone, disulfiram with placebo, or disulfiram with naltrexone. Although there were no interactions of any treatment with the Asn40Asp SNP, the *DBH* SNP interacted with naltrexone on the primary outcome of abstinence from heavy drinking. Specifically, naltrexone-treated individuals who were carriers of the *DBH* rs1611115*T-allele were significantly more likely to not drink heavily than C-allele homozygotes. Similarly, among participants receiving disulfiram treatment, *DBH* T-allele carriers reported fewer drinks per drinking day than C-allele homozygotes.

Other dopaminergic gene polymorphisms may also moderate alcohol pharmacotherapy effects. The ankyrin repeat and kinase domain containing 1 (*ANKK1*) Taq1A polymorphism (rs1800497) is a C to T substitution. Although the SNP was originally believed to map to *DRD2*, it is 10 kb downstream of the gene and results in a non-synonymous substitution in the adjacent gene, *ANKK1* (Neville et al. 2004). The polymorphism is associated with up to a 30% reduction in D2 receptor density, decreased dopamine receptor sensitivity, and elevated dopamine transporter (DAT) density (Noble et al., 1991; Pohjalainen et al., 1998; Schellekens et al., 2012). Its association with alcohol dependence is under debate (for reviews see Noble, 1998; Wang et al., 2013).

Bromocriptine, a dopamine agonist, was investigated as a therapeutic agent for alcohol dependence. Lawford et al. (1995) examined the alcohol treatment potential of bromocriptine and the Taq1A polymorphism as a moderator of treatment response. They treated 83 alcohol-dependent inpatients with bromocriptine (7.5 mg/day) or placebo. They found that the greatest reductions in craving and anxiety were found in bromocriptine-treated alcoholics who were C-allele carriers (i.e., A1/A1 or A1/A2 genotype). Because the study was limited to inpatients, there was no reported drinking, so whether the polymorphism moderated bromocriptine's effects on drinking was not evaluated.

GABAergic and Glutamatergic Genes

Ooteman and colleagues (2009) assigned alcohol-dependent patients (n = 126) to treatment with either naltrexone (50 mg/day) or acamprosate (1.3-2.0 g/day) in which participants completed a cue exposure experiment before starting medication and after three weeks of treatment. Polymorphisms in dopamine, opioid, glutamate and GABA receptor gene polymorphisms were examined in relation to reductions in cue-induced craving and physiological reactivity. The authors reported moderating effects of polymorphisms at *ANKK1* (Taq1A), *GABRB2* (C1412T) and *GABRA6* (T1519C), though most findings failed to reach the conventional significance level of <0.05 and there was no effort to correct for multiple testing, rendering the findings uninterpretable.

Recently, Kranzler et al. (2014) randomly assigned 138 heavy drinkers to receive 12 weeks of treatment with topiramate or matching placebo. Based on prior research showing an association of rs2832407, a SNP in *GRIK1*, which encodes the kainate GluK1 receptor subunit, to alcohol dependence (Kranzler et al. 2009), they examined the moderating effects of the SNP in the European-American subsample (N=122). They found that topiramate's

reduction of heavy drinking days was significantly greater than that of placebo only in rs2832407*C-allele homozygotes. In contrast to an earlier report by Ray et al. (2009) that this SNP moderated topiramate's adverse effects in non-treatment-seeking heavy drinkers, Kranzler et al. did not see a moderating effect of the SNP on either individual adverse effects or an aggregate measure of these.

Because acamprosate shares structural similarities with glutamate, which activates the N-methyl-D-aspartate (NMDA) receptor, genes encoding proteins in this system have been investigated with respect to acamprosate treatment response (Chabenat et al., 1988). In a recent three-month acamprosate trial in a sample of 225 alcohol-dependent subjects (Karpyak et al., 2014), the length of abstinence was associated with two polymorphisms (rs2058878, rs2300272) in *GRIN2B*, which encodes the GluN2B subunit of the NMDA receptor. Among acamprosate-treated alcoholics, the minor A allele of rs2058878 was associated with a longer duration of abstinence, while the minor rs2300272 G allele was associated with a shorter duration of abstinence.

Serotonergic Genes

SLC6A4, which encodes the serotonin transporter, a membrane protein that transportsserotonin from the synaptic cleftback to the presynaptic neuron, is the most studied of the serotonin system genes. A functional insertion-deletion polymorphism in the promoter region of the gene yields a lower activity short (S) allele and a higher activity long (L) allele (Nakamura et al., 2000). An A to G SNP has also been identified in the L allele, yielding a tri-allelic genotype (S, L_A, and L_G), in which the L_G allele is functionally similar to the low-activity S allele (Hu et al., 2006). Moderator analyses of serotonergic medications have used both the bi-allelic (S vs. L) and the tri-allelic (S′, which includes both S and L_G allels, vs. L′, which comprises only the L_A allele) genotypes.

Kranzler et al. (2011) examined the effects of the 5-HTTLPR tri-allelic genotype on the response to sertraline (200 mg/day) in 134 individuals with early-onset or late-onset alcohol dependence. They found that the moderating effect of age of onset on the response to sertraline was conditional on genotype. There were no main or interaction effects among S′ allele carriers. However, in L′ homozygotes, at the end of treatment, late-onset alcoholics reported fewer drinking and heavy drinking days when treated with sertraline, while early-onset alcoholics had fewer drinking and heavy drinking days when treated with placebo.

In a study of the selective 5-HT3 antagonist ondansetron (4 μg/kg twice daily) (Johnson et al. 2011), 283 alcohol-dependent individuals were randomized to receive either active medication or placebo based on the bi-allelic 5-HTTLPR polymorphism (LL vs. S-allele carrier). This study also examined the moderating effect of a SNP in the 3′ untranslated region of *SLC6A4* (rs1042173). 5-HTTLPR L-allele homozygotes treated with ondansetron reported fewer heavy drinking days and more abstinent days than those receiving placebo. Further, individuals who were also rs1042173*T-allele homozygotes showed the greatest reductions in drinking outcomes compared to the remaining genotype by medication groups combined (Johnson et al., 2011). In a secondary analysis of this study, Johnson et al. (2013) genotyped SNPs in the 5-HT3 receptor genes, *HTR3A* and *HTR3B*, and evaluated the optimal combination of genotypes to predict the response to ondansetron treatment. They

found that, in addition to the two polymorphisms in *SLC6A4*, response to ondansetron treatment was also significantly greater than for placebo in individuals with one or more of the following genotypes: rs1150226-AG and rs1176713-GG in *HTR3A*, or rs17614942-AC in *HTR3B*. They calculated that the use of these five genotypes would identify 34% of European Americans with alcohol dependence who are likely to respond very favorably to ondansetron treatment.

Discussion

The studies reviewed here provide preliminary evidence that genetic variation moderates the effects of a number of medications used to treat AUD. Despite promising initial findings, however, no specific candidate polymorphism has to date yielded replicable findings.

A leading candidate for genetic moderation, the Asn40Asp SNP in *OPRM1*, has been shown in some, but not all, human laboratory studies to moderate the effects of alcohol or of naltrexone's modification of alcohol's effects. Although human laboratory studies may help to elucidate the mechanism by which effects such as differential reduction of alcohol's euphoric effects or of craving may be moderated by genetic variation, they do not provide direct or causative evidence of genetic differences in the effectiveness of a medication to prevent relapse or decrease alcohol use. The ultimate utility of a pharmacogenetic effect requires demonstration in a clinical trial.

Analytic approaches that seek to combine the effects of multiple studies via meta-analysis are being used with increasing frequency. Enhanced meta-analytic methods may improve our ability to predict treatment outcome based on genotype. Although some clinical trials have shown that the Asn40Asp SNP moderates the effects of naltrexone, the first prospective trial in which assignment to naltrexone or placebo was stratified on genotype recently failed to show an interaction with naltrexone treatment (Oslin et al., 2014). This study followed the publication of a meta-analysis that showed a doubling of the efficacy of naltrexone in Asp40-allele carriers (Chamorro et al., 2012). This raises questions about the validity of meta-analytic findings based on secondary analyses of pharmacogenetic effects. Publication bias, wherein negative studies are not published, may contribute to this problem. Irrespective of the basis for the contradictory findings, it appears that there may be no substitute for large, prospective clinical trials to advance the pharmacogenetics of AUD treatment.

Another important issue to be addressed in the pharmacogenetics of AUD is the use of appropriate statistical methods of analysis, e.g., the need to correct for multiple testing, which is of particular concern given the ready availability of genotyping. Failure to correct for multiplicity appears to be an important source of false positive findings and the associated failure to replicate the results of candidate gene studies (Hart et al., 2013; Munafo et al., 2007). Clinical pharmacogenetic studies must also recognize and control for sample heterogeneity (Johnson, 2010; Leggio et al., 2009; Pombo and Lesch, 2009), which has often been ignored in the many published pharmacogenetic studies that represent secondary analyses of medications trials. For example, the allele frequencies of many of the study's primary target variants may differ substantially by population group, as with the often-

studied *OPRM1* A118G SNP (Hastie et al., 2012). This may adversely affect power due to an imbalance in sample size or confound the analysis through undetected population structure. Pharmacogenetic differences among individuals in their capacity to metabolize alcohol are also generally not taken into account. The field would also greatly benefit from the standardization of treatment outcome measures. In the final analysis, our limited understanding of the etiology of AUD undermines our efforts to design pharmacogenetic studies that address key dimensions of the disorder.

This review of the literature on the genetic moderation of subjective effects of alcohol and pharmacotherapy for AUD identifies a number of promising areas for further study. Not surprisingly, given the novelty of the field and the variety of methods used in the studies to date, some findings have not been replicated. Thus, to date, the clinical impact of pharmacogenetics in alcohol studies is limited. Despite this limitation, the great potential that exists for clinical advances through pharmacogenetics argues strongly for continued efforts to elucidate genetic risk factors for AUD and improve pharmacotherapeutic options for heavy drinkers through personalized treatment. We are confident that the field will eventually have a significant public health impact. Ultimately, pharmacogenetics should enable us to identify individuals who are most likely to respond favorably to a particular medication and those who are most likely to suffer treatment-limiting adverse effects, both of which are important contributors to personalized care.

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Table 1

Pharmacogenetic trials for the treatment of Alcohol Use Disorder

Gene Name	Polymorphism	Medication	Sample Size	Population	Treatment × Genotype Interaction* ↑ Greater efficacy ↓ Less efficacy ↔ No interaction	Citation
ANKK1	Taq1A: rs1800497	Bromocriptine	52	Australian	↑ CT/TT genotypes	Lawford et al. (1995)
DBH	rs1611115	Disulfiram, Naltrexone	107	European-American	Disulfiram: ↑ CC Naltrexone: ↑ CT/TT	Arias et al. (2014)
DRD1	rs686	Acamprosate, Naltrexone	108	Dutch	↔	Ooteman et al. (2009)
OPRD1	rs2234918	Naltrexone	215	Caucasian- and African-American	↔	Gelernter et al. (2007)
	rs678849	Naltrexone	215	Caucasian- and African-American	↔	Gelernter et al. (2007)
	rs2234918	Nalmefene	272	Central European and Finnish	↔	Arias et al. (2008)
	rs678849	Nalmefene	272	Central European and Finnish	↔	Arias et al. (2008)
	rs4654327	Naltrexone	40	Majority Caucasian	↑ A allele carriers	Ashenhurst et al. (2012)
OPRK1	rs963549	Naltrexone	215	European and African American	↔	Gelernter et al. (2007)
	rs963549	Nalmefene	272	Central European and Finnish	↔	Arias et al. (2008)
	rs997917	Naltrexone	40	Majority Caucasian	↑ TT genotype	Ashenhurst et al. (2012)
OPRM1	*Asn40Asp (A118G)*: rs1799971	Naltrexone	141	Majority European Descent	↑ G-allele carriers	Oslin et al. (2003)
	rs1799971 rs6848893	Naltrexone	215	Caucasian and African-American Males	↔	Gelernter et al. (2007)
	rs1799971	Naltrexone	604	European	↑ G-allele carriers	Anton et al. (2008)
	rs1799971	Nalmefene	272	Central European and Finnish	↔	Arias et al. (2008)
	rs1799971	Naltrexone	63	Korean	↑ G-allele carriers	Kim et al. (2009)
	rs1799971	Naltrexone, Acamprosate	108	Dutch	↔	Ooteman et al. (2009)
	rs1799971	Naltrexone	158	Male and Female. 153 European-Americans.	↑ G-allele carriers	Kranzler et al. (2013)
	rs6848893	Nalmefene	272	Central European and Finnish	↔	Arias et al. (2008)
	rs1799971	Disulfiram, Naltrexone	107	European-American	↔	Arias et al. (2014)

Gene Name	Polymorphism	Medication	Sample Size	Population	Treatment × Genotype Interaction* ↑ Greater efficacy ↓ Less efficacy ↔ No interaction	Citation
GABRA6	T1519C	Naltrexone, Acamprosate	108	Dutch	↑ T-allele carriers receiving naltrexone ↑ C-allele carriers receiving acamprosate	Ooteman et al. (2009)
GABRG2	G3145A: rs211013	Naltrexone, Acamprosate	108	Dutch	↔	Ooteman et al. (2009)
GRIK1	Rs2832407	Topiramate	122	European-American	↑ CC genotype	Kranzler et al. (2014)
GRIN2B	C2664T: rs1806201	Naltrexone, Acamprosate	108	Dutch	↔	Ooteman et al. (2009)
	rs2058878 rs2300272	Acamprosate	225	European-American	↑ rs2058878 (minor A allele) ↓ rs2300272 G allele	Karpyak et al. (2014)
SLC6A4	5-HTTLPR	Sertraline	134	92% European	↑ LL genotype	Munafo et al. (2006)
	5-HTTLPR rs1042173 (T/G)	Ondansetron	283	European-American	↑ LL genotype ↑ LL + TT (rs1042173)	Johnson et al. (2011)
SLC6A4 HTR3A HTR3B	5-HTTLPR rs1042173 + numerous *HTR3A&B* SNPs	Ondansetron	283	European-American	↑ *HTR3A* (rs1150226, AG) ↑ *HTR3A* (rs1176713, GG) ↑ *HTR3B* (rs17614942, AC) ↑ LL + TT (rs1042173)	Johnson et al. (2013)