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Pharmacogenetics of Alcohol and Alcohol Dependence Treatment

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Abstract

In this article, we review studies of genetic moderators of the response to medications to treat alcohol dependence, the acute response to alcohol, and the response to the psychotherapeutic treatment of heavy drinking. We consider four neurotransmitter systems: opioidergic, dopaminergic, GABAergic, and glutamatergic and focus on one receptor protein in each: *OPRM1* (the μ-opioid receptor gene), *DRD4* (the D_4 dopamine receptor gene), *GABRA2* ($GABA_A$ receptor α-2 subunit gene), and *GRIK1* (the kainite receptor GluR5 subunit gene). We conclude that because parallel developments in alcoholism treatment and the genetics of alcohol dependence are beginning to converge, using genotypic information, it may be possible to match patients with specific treatments. Of greatest clinical relevance is the finding that the presence of an Asp40 allele in *OPRM1* modestly predicts a better response to naltrexone treatment. Promising findings include the observations that a polymorphism in *GABRA2* predicts the response to specific psychotherapies; a polymorphism in *DRD4* predicts the effects of the antipsychotic olanzapine on craving for alcohol and drinking behavior; and a polymorphism in *GRIK1* predicts adverse events resulting from treatment with the anticonvulsant topiramate. Although variants in other genes have been associated with the risk for alcohol dependence, they have not been studied as moderators of the response either to treatment or acute alcohol administration. We recommend that, whenever possible, treatment trials include the collection of DNA samples to permit pharmacogenetic analyses, and that such analyses look broadly for relevant genetic variation.

INTRODUCTION

Although the sequencing of the human genome and the substantial advances in genomic medicine that have resulted from it have begun to influence the treatment of alcohol

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DISCLOSURE

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dependence, to date, the clinical impact has been limited. In coming years, the insights gained from genetics into the etiology and pathophysiology of alcohol and other substance dependence are likely to alter substantially the treatment of these disorders. As in other areas of medicine, the identification of novel drug targets and a greater understanding of disease mechanisms will contribute to the rational design of pharmacotherapeutic agents for substance dependence. The potential benefits of the application of genetics to alcohol dependence treatment can be seen in a growing number of studies that have aimed to match specific treatments to patients (i.e., personalized medicine) based on variation in candidate genes. Specifically, this approach has sought to identify genetic moderators of the response to medications and the mechanisms of such effects.

In this review, we discuss the pharmacogenetics of alcohol and alcohol dependence, which extends our prior review [1]. There is a growing literature on genetic risk factors for alcohol dependence [2], however, we limit our discussion of these factors to those with direct relevance to pharmacogenetics. Although the main focus of the review is on studies of genetic moderators of the response to medications to treat alcohol dependence, we also discuss genetic moderation of the acute response to alcohol, which can provide functional validation of findings from population studies showing that genetic variation influences the risk or course of alcohol dependence. We also briefly discuss an effort to identify genetic moderators of the response to the psychotherapeutic treatment of alcohol dependence, an area of considerable clinical importance, since the majority of alcohol treatments are psychosocial in nature.

The Opioidergic System

Opioid Receptors and the Effects of Alcohol and Drugs—Three classes of opioid receptors, μ, κ, and δ, interact with opioid peptides to produce their biological effects [3]. Opioid receptors belong to a family of G-protein coupled receptors that are functionally coupled to adenyl cyclase. The human genes encoding the μ-opioid receptor (*OPRM1)*, the δ opioid receptor (*OPRD1)*, and the κ opioid receptor (*OPRK1)* are all expressed in the brain. Endorphins, dynorphins, and enkephalins are the primary endogenous ligands for the μ, κ, and δ receptors, respectively, and are encoded by *POMC*, *PDYN* and *PENK*. An opiate receptor-like 1 protein, encoded by *OPRL1* [4], has also been identified; its primary ligand is the nociceptin/orphanin FQ neuropeptide [5, 6].

Although the opioid receptors are highly homologous, they have different anatomical distributions [7] and pharmacological profiles [8]. The μ-opioid receptor is a key mediator of the effects of many opioid agonists [9]. μ-opioid receptors in the ventral tegmental area (VTA) regulate the activity of dopaminergic neurons in the nucleus accumbens (NAc). Infusion of a μ receptor agonist into the VTA increases dopamine release in the NAc, while infusion of a μ receptor antagonist decreases dopamine release [10]. Mice lacking the μ-opioid receptor [11, 12] show a loss of morphine-induced analgesia, reward, and withdrawal symptoms. The μ-opioid receptor also plays a role in the rewarding properties of ethanol and other drugs of abuse, effects that may be mediated by these drugs' capacity to increase dopamine release in medial forebrain structures [13]. Mice lacking the μ-opioid receptor self-administer less alcohol than wild type mice [14].

The δ opioid receptor also modulates alcohol consumption [15, 16]. In rats selectively bred for high alcohol drinking, the selective δ antagonist, ICI-174864, was more potent than naloxone in suppressing alcohol consumption [15]. The finding with ICI 174864 was subsequently replicated and the more highly selective and longer-acting δ antagonist, naltrindole hydrochloride, produced a dose-dependent suppression of drinking in rats selectively bred for alcohol consumption [16]. Mice lacking the δ opioid receptor self-administer more alcohol than wild type mice [17]. Mice lacking the κ opioid receptor have been shown to have a lower preference for alcohol [18], and variation in *OPRK1* has been associated with alcohol dependence[19-21].

The effects of selective agonist administration are blocked by the administration of selective μ and δ receptor antagonists. In the CNS, δ agonists modulate μ-receptor mediated analgesia, which suggests that there is cross-talk between these opioid receptor subtypes [22]. Administration of a selective κ agonist decreased dopamine release in the NAc, an effect that was blocked by a selective κ antagonist [23]. Because opioid antagonists such as naltrexone antagonize δ and κ receptors, as well as μ-opioid receptors, the genes encoding the δ and κ receptors (*OPRD1* and *OPRK1*) may also moderate the effects of this class of drugs.

Variation in Opioidergic Genes Moderates the Pharmacologic Effects of Opioid Antagonists—The most widely studied genetic moderators of alcohol treatment response are variants in genes encoding the opioid receptor proteins. Bergen et al. [24] identified a common single nucleotide polymorphism (SNP) in exon 1 of *OPRM1*, A118G, which produces an amino acid substitution (Asn40Asp) in the N-terminal extracellular domain of the receptor. The allele frequency at this locus varies widely in different populations. The Asp40 (118G) allele shows the lowest frequency in African-Americans (<5%), an intermediate frequency in people of European ancestry (2.5-15.5%), and the highest frequency in Asians (25–47%) [25]. When expressed in AV-12 cells, μ opioid receptors containing the Asp40 allele had three times the binding affinity for β-endorphin (but not other ligands) of μ opioid receptors containing the Asn40 allele and they were three-fold as potent in activating G protein-coupled potassium channels when expressed in *Xenopus* oocytes [26]. In contrast, studies of the Asp40 allele expressed in other cell lines have either shown little effect or a 1.5-fold lower transcription rate and more than 10-fold lower protein levels than with the Asn40 allele [27]. Thus, the physiological effect of this variation on receptor function in human brain is not clear.

Ray and Hutchison [28] found that heavy drinkers with the *OPRM1* Asp40 allele experienced a more intense “high” and greater subjective intoxication, stimulation, sedation, and happiness following intravenous alcohol administration and were also more likely to report a family history of an alcohol use disorder than Asn40 homozygotes. In a cue exposure study, male heavy drinkers with an Asp40 allele reported higher levels of craving following exposure to an alcohol stimulus than did Asn40 homozygotes [29].

Several human laboratory studies have shown that the Asn40Asp SNP moderates responses to μ-opioid receptor antagonists. The hypothalamic-pituitary-adrenal (HPA) axis is activated by antagonism of the opioid receptor. Healthy subjects with an Asp40 allele had a greater

cortisol response to the opioid antagonist naloxone [30-32]. Hernandez-Avila et al. [32] found that European-American (EA) participants with one or two Asp40 alleles had a significantly greater cortisol response to naloxone than Asn40 homozygotes, but individuals of Asian ancestry did not. This suggests that the association between the Asn40Asp and the HPA-axis response to naloxone is not explained fully by the Asn40Asp amino acid substitution. Other *OPRM1* variants [33] that are in linkage disequilibrium with the Asn40Asp SNP may explain some of the effects associated with that polymorphism. Variation in other genes that balance the effects of the Asn40Asp SNP may also exist and could differ by population. Further, McGeary et al. [34] reported a paradoxical increase in cue-elicited craving among heavy drinkers with an Asp40 allele following pretreatment with naltrexone, while no change in craving was noted among Asn40 homozygotes.

Ray and Hutchinson [35] used a within-subject, double-blind, placebo-controlled laboratory study to examine the effects of pre-treatment with naltrexone or placebo on the response to intravenous alcohol in a sample of non-treatment-seeking heavy drinkers. They found that individuals with one or two Asp40 alleles reported lower levels of alcohol craving and greater alcohol-induced “high” with higher breath alcohol concentrations. Further, naltrexone blunted the positive response to alcohol, particularly among individuals with the Asp40 allele.

Opioid Receptor Antagonists and Alcoholism Treatment—Although meta-analyses of alcohol dependence treatment [36, 37] show clearly that naltrexone is superior to placebo on a number of drinking outcomes, there is considerable variability in efficacy among studies. Even in studies in which the naltrexone group shows better outcomes than the placebo group, the medication is not efficacious for all patients who receive it. The variable treatment response underscores the need to identify which individuals respond best to naltrexone therapy and the processes by which the medication exerts its therapeutic effects. Efforts to identify clinical features that moderate the naltrexone response have shown that a family history of alcohol dependence is the most consistent predictor, such that individuals having a greater percentage of alcoholic family members show a more robust treatment response [38-40]. Thus, it may be possible to identify genetic variation that can be used to identify which alcohol-dependent individuals are most likely to benefit from opioid antagonist treatment.

A number of studies have been conducted examining variation in *OPRM1* as a moderator of the response to treatment with naltrexone in treatment-seeking alcoholics (see Table 1). Oslin et al. [41], in a study of 130 EA subjects from three placebo-controlled trials of naltrexone, found that patients with one or two Asp40 alleles who received the active medication were significantly less likely than Asn40 homozygotes to relapse to heavy drinking. Although a formal interaction was not detected, placebo-treated subjects showed no moderating effect of genotype. Gelernter et al. [42] examined the moderating effect of the Asn40Asp polymorphism, two other *OPRM1* SNPs, three markers in *OPRD1*, and one marker in *OPRK1* on treatment response in a subsample of patients from the VA Cooperative Study of Naltrexone Treatment [43]. They found no evidence of genetic moderation of the response to naltrexone treatment. In 297 EA participants from the COMBINE Study, there was a positive moderating effect of the Asp40 allele on the

response to naltrexone [44]. This effect was seen both on the percentage of heavy drinking days and on a global measure of treatment outcome. In a study of 63 treatment-seeking Korean alcoholics who were treated with naltrexone [45], 32 subjects were determined to be treatment adherent. In this sub-sample, individuals with one or two copies of the Asp40 allele showed a longer time to relapse (defined as the first day on which men drank ≥ 5 drinks and women drank ≥ 3 drinks) than Asn40 homozygotes.

The Asn40Asp has also been examined in studies of naltrexone conducted in non-treatment seeking heavy drinkers. In a brief, placebo-controlled, cross-over trial of naltrexone in a group of 30 subjects, although Mitchell et al. found that naltrexone reduced drinking behavior, they did not find a moderating effect of the Asp40 allele [46]. Similarly, Tidey et al. [47] found no moderating effect of the Asp40 allele on drinking outcomes in a brief, placebo-controlled trial of naltrexone in 173 heavy drinkers.

The moderating effects of polymorphic variation in opioid receptor genes has also been examined in relation to treatment response in a study of nalmefene, a specific and potent opioid antagonist with affinity for all three of the opioid receptor subtypes. Arias et al. [48] genotyped two SNPs in *OPRM1* (including Asn40Asp), two SNPs in *OPRD1*, and one SNP in *OPRK1* in a sub-sample of alcohol-dependent patients from a placebo-controlled trial of nalmefene [49]. As in the initial trial, in the pharmacogenetic sub-sample, nalmefene significantly reduced the weekly number of heavy drinking and very heavy drinking days. However, none of the genotypes examined showed either a main effect on drinking or a moderating effect on the nalmefene-related drinking reduction.

Summary—Overall, there appears to be a modest effect of the *OPRM1* Asn40Asp SNP to moderate the efficacy of naltrexone, particularly the medication's effects on risk of heavy drinking. However, there are considerable differences among studies. There is no evidence of a moderating effect of the SNP on the effects of nalmefene, but to date there has only been one pharmacogenetic study of that medication. An important factor in these and other pharmacogenetic studies is the limited statistical power resulting from both the small samples and the imbalance in the frequency of the alleles being studied. Further, because the designs of the various studies of *OPRM1* have differed substantially from one another (e.g., different subject populations, different outcome measures, and differences and limitations in which genetic variants were analyzed), the data are not amenable to meta-analysis. Consequently, large, prospective studies of the effects of a wider range of variations in the opioid genes are needed to estimate more accurately the magnitude of its moderating effects on the efficacy of naltrexone.

The Dopaminergic System

Mesolimbic dopaminergic neurons that project from the VTA to the NAc mediate the reinforcing effects of alcohol [50]. Because alcohol administration enhances dopamine release in the NAc [51], variants in genes encoding several proteins involved in dopaminergic neurotransmission, including the D_2 and D_4 dopamine receptors have been examined for their association to the subjective effects of alcohol and the risk of alcohol

dependence. These receptors are homologous, both belonging to the D_2 receptor family; they are encoded by *DRD2* and *DRD4*, respectively.

Considerable research attention has been devoted to the role of the D_2 dopamine receptor in the effects of alcohol and risk for alcohol dependence [50]. Subjects with early-onset alcohol dependence were found to have lower dopamine D_2 availability in the caudate and putamen than control subjects [52]. Alcoholic subjects also were found to have lower D_2 receptor levels in the ventral striatum than controls [53]. Further, striatal D_2 receptor concentrations were negatively correlated with alcohol craving when these subjects were presented with alcohol-related cues [53].

Over the past 20 years, a substantial literature has developed concerning the association of alcohol dependence with the "TaqI A" polymorphism (rs1800497) on chromosome 11q, in the region of *DRD2* [2]. Although this polymorphism was initially thought to be located in the 3' region of *DRD2*, it has more recently been shown to lie within a neighboring gene, *ANKK1* (ankyrin repeat and kinase domain containing 1), where it results in an amino acid substitution [54]. Recent studies [55, 56] have shown that variation in *ANKK1* is more strongly associated with alcohol dependence than variation in *DRD2*, suggesting that prior findings of association with rs1800497 may reflect functional variation in *ANKK1*.

In a double-blind, placebo-controlled study of bromocriptine, a D_2 agonist, in a sample of alcoholics who were genotyped for this polymorphism, individuals with one or two copies of the TaqI A1 allele showed greater decreases in craving and anxiety when treated with bromocriptine, while those receiving placebo had a higher rate of attrition [57]. The relevance of these findings for drinking behavior is very limited, however, since the study was conducted in an inpatient setting and no effort was made to follow the patients after discharge.

A number of studies have examined the effects of variation in *DRD4*, which encodes the D_4 dopamine receptor, on the response to alcohol cue exposure and alcohol administration, and as a moderator of the effects of medication or psychotherapy on these responses. *DRD4* contains a 48-basepair variable number of tandem repeats (VNTR) polymorphism in exon III, with 2, 4, and 7 repeats being most common; the 7-repeat (i.e., long or L) allele is associated with a lower intracellular response to dopamine than the short (S) variants (i.e., those with fewer than 7 repeats) [58].

Using a human laboratory paradigm, the L allele of *DRD4* has been associated with alcohol craving or drinking in some [59-62], but not all [34, 63], studies. In one study, following acute treatment with the D_2/D_4 antagonist olanzapine (5 mg) and a priming dose of alcohol [60], heavy drinking participants reported less craving than they did following pretreatment with an active control medication (cyproheptadine). However, in this study, olanzapine reduced craving after exposure to alcohol cues only among individuals with one or two copies of the L allele. Similar findings were obtained in a study that combined cue-elicited craving with treatment for alcohol dependence in a 12-week, randomized, placebo-controlled trial of olanzapine. After two weeks of treatment, participants with one or two copies of the L allele who were treated with olanzapine reported reduced cue-elicited

craving. Among individuals with an L allele, the active medication also resulted in less drinking over the course of the 12-week trial. There were no such effects of the medication among individuals homozygous for an S allele.

The VNTR has also been shown to moderate treatment with a single session of motivational enhancement therapy in problem drinkers [64]. In that study, individuals homozygous for the S allele of the VNTR showed greater behavior change, which consisted of taking steps toward reducing drinking following the MET compared with an educational intervention.

Summary—Animal and human studies have implicated the dopaminergic system in the reinforcing effects of alcohol. Association studies of dopaminergic genes have focused primarily on the TaqI A polymorphism, which has been shown to reside in the *ANKK1* gene that is adjacent to *DRD2*. There are variable findings in the literature concerning the association of this gene to alcohol dependence. The L allele of a VNTR in *DRD4*, which encodes the D_4 dopamine receptor, has been shown in some studies to moderate the response to alcohol-related cues and in treatment studies to moderate the effects of the antipsychotic medication olanzapine and motivational enhancement therapy. Research is needed to evaluate the role of *ANKK1* variants as moderators of the effects of alcohol and of treatments for heavy drinking and alcohol dependence. Because much of the research on the moderating effects of the VNTR in *DRD4* has focused on self-reported craving for alcohol, further research on these variants is needed to examine their effects on drinking behavior.

The γ-aminobutyric Acid (GABA) System

Variation in genes encoding proteins in the γ-aminobutyric acid (GABA) neurotransmitter system appears to moderate the effects of alcohol. There are two major classes of GABA receptors: $GABA_A$ receptors, which are pentameric ionotropic ligand-gated receptors linked to chloride channels, and $GABA_B$ receptors, which are G-protein coupled metabotropic receptors. $GABA_A$ receptors are the principal site of action of benzodiazepines, which increase chloride conductance in response to GABA binding, thus hyperpolarizing and inhibiting cell firing. The $GABA_A$ receptor is also an important site of action of endogenous neurosteroids and plays an important role in several behavioral effects of alcohol.

Several subunits of $GABA_A$ receptors have been implicated in ethanol's action in pharmacological studies, and genes encoding $GABA_A$ subunits have been candidates for association to alcohol dependence. Of particular interest here is the $GABA_A$ α2 subunit, which is encoded by the *GABRA2* gene. Porjesz et al. [65] reported linkage of EEG beta frequency to chromosome 4p and linkage disequilibrium to a $GABA_A$ receptor cluster on that chromosome in a sample of multiplex alcohol dependence families. Fine mapping of this region showed allelic and haplotypic association to *GABRA2* [66]. In this analysis, SNPs throughout *GABRA2*, but not the other three members of the gene cluster, were associated with AD. Subsequent case-control studies replicated this finding, providing evidence of association to alcohol dependence [67-71]. Enoch et al. [72] reported a significant association to *GABRA2*, but only when differentiating alcohol-dependent individuals into two groups using a measure of dimensional anxiety (i.e., harm avoidance). Soyka et al. [73] reported an association of alcohol dependence to different variants than those associated

with that phenotype in prior studies. There have also been non-replications of the association [74, 75]. The adjacent gene on chromosome 4p, *GABRG1*, which encodes the gamma-1 subunit, has also been associated with alcohol dependence in EAs, Plains Amerindians, and Finns [67, 76] and with the response to alcohol [77].

No specific causative variant or biological mechanism has been identified for the association of alcohol dependence to *GABRA2*. A study of finasteride, which blocks the synthesis of some neuroactive steroids, showed that healthy subjects with one or two copies of the alcohol dependence-associated G-allele of the *GABRA2* SNP rs279858 [66, 68-70], showed a blunted subjective response to the stimulating and anesthetic effects of acute alcohol [78]. In this study, homozygotes for the low-risk A-allele at this SNP reported significantly less subjective effects during the finasteride session compared to the placebo session [78]. These findings provide indirect evidence of a mediating role for neuroactive steroids in some of the subjective effects of alcohol and suggest that the risk of alcoholism associated with *GABRA2* may be related to differences in the subjective response to alcohol. Haughey et al. [79] measured GABA alpha-2 subunit mRNA expression in post-mortem brain tissue. Although they found no difference in mRNA levels in prefrontal cortex as a function of diagnosis (alcoholic vs. control), A-allele homozygotes had significantly greater mRNA expression than heterozygotes. These investigators [79] also examined the subjective effects of oral and intravenous alcohol administration in moderate-to-heavy drinkers. In the oral alcohol administration study, G-allele homozygotes reported significantly greater alcohol-induced positive mood and both homozygote groups reported significantly greater alcohol-induced vigor than the heterozygotes [78]. In the intravenous administration study, G-allele homozygotes reported significantly greater alcohol-induced stimulation than heterozygotes and a significantly greater hedonic value of alcohol compared with the other two genotype groups [78]. Findings from these two alcohol administration studies are not wholly consistent with one another, which may be have resulted from differences in study design and the dependent measures that were employed.

Bauer et al. [80], in a secondary analysis of data from Project MATCH, a longitudinal study of psychotherapy for alcoholism, found that individuals with the one or two copies of the high-risk *GABRA2* G-allele (rs279858) had higher daily probabilities of drinking and heavy drinking than A-allele homozygotes. Interestingly, the polymorphism also moderated the response to the specific psychotherapies examined in the study. Although this was an exploratory analysis, it showed that among individuals homozygous for the low-risk (A) allele, Twelve-step Facilitation yielded better drinking outcomes than Cognitive-Behavioral Therapy or Motivational Enhancement Therapy. This finding requires replication in other samples, but in view of the high reliance on psychotherapy in alcoholism rehabilitation, it has important implications for the treatment of alcohol dependence.

Other GABA-receptor genes have also been associated with risk for alcoholism or in sensitivity to the effects of alcohol, including *GABRA1* [81], *GABRG3* [82], and *GABRR1* and *GABRR2* [83]. Together, these results provide evidence that variation in genes encoding $GABA_A$ receptor subunits contributes to risk of alcohol dependence, with the greatest evidence for association for genes on chromosome 4, particularly *GABRA2*.

Summary—Although *GABRA2* has been associated with alcohol dependence risk, the causative variant or variants that modulate that risk remain to be identified. In view of evidence of association at the adjacent gene, *GABRG1*, it also remains to be determined whether the functional effects are limited to one or both of these genes. Other genes in the $GABA_A$ system appear also to be associated with alcohol dependence risk. To date, however, there are no pharmacotherapy trials that have comprehensively examined variation in these genes as moderators of the response to alcohol treatment. Nonetheless, a *GABRA2* variant has been shown to predict the subjective response to alcohol in healthy subjects and long-term outcomes in subjects participating in Project MATCH, a study of the psychotherapeutic treatment of alcoholism. The preliminary finding of a moderating effect of a SNP in *GABRA2* on the response to psychotherapy requires replication before it could be considered to be of clinical value.

The Glutamatergic System

Glutamate is the most abundant excitatory neurotransmitter in the central nervous system. Glutamatergic neurotransmission has been implicated in the risk for alcohol dependence and its pharmacologic treatment. Kalivas [84] has elaborated a glutamate homeostasis hypothesis of addiction that attributes the failure to control drug-seeking behavior (i.e., impaired control in the alcohol dependence syndrome of Edwards and Gross [85]) to an enduring imbalance between synaptic and non-synaptic glutamate produced by chronic substance use. The imbalance is thought to impair communication between the prefrontal cortex and the nucleus accumbens, thereby contributing to impaired control over substance use. To the extent that this hypothesis can be applied to chronic heavy drinking, glutamatergic treatments and other approaches aimed at reversing these changes could help to restore the disrupted control over drinking behavior that is a key element of alcohol dependence.

Consistent with this hypothesis, the attenuation of glutamatergic effects reduces alcohol-induced reward and relapse-like behavior in animals [86]. Several studies have examined the association of genes encoding glutamate receptor subunits with alcohol dependence, with the NMDA receptor type receiving the most attention. A survey of 10 glutamate system genes showed a moderate association with alcohol dependence (i.e., an odds ratio of 2.18) of markers in *GRIN2A*, which encodes NR2A, the N-methyl-D-aspartate receptor subunit 2A [87]. That study did not, however, examine other glutamate receptor subunit genes. For example, kainate receptors are important modulators of interneuron excitability in the hippocampus. Ethanol has been shown to be a potent inhibitor of this effect at plasma concentrations that result from the ingestion of 1-2 alcoholic drinks, an effect that appeared to be specific for kainate receptors and physiologically relevant [88].

Trials of medications that alter glutamatergic activity, including acamprosate [89] and topiramate [90, 91], are consistent with the idea that glutamate plays a central role in the pathophysiology and treatment of alcohol dependence. Kainate receptors are tetramers assembled from subunits including GluR5, GluR6, and GluR7 [92]. Different combinations of subunits and splice variants have different regional distributions and physiologic properties.

Of particular interest as genetic moderators of glutamatergic medications, kainate receptors containing certain subunits, including GluR5 and GluR6, selectively bind topiramate [93, 94]. Kranzler et al. [95] examined polymorphic variation in *GRIK1*, which encodes the GluR5 subunit, on the hypothesis that evidence of association to alcohol dependence could implicate this gene in moderating the effects of topiramate in the treatment of alcohol dependence. *GRIK1* consists of 18 exons and maps to chromosome 21q22.11. Because the gene is too large to examine it comprehensively, the study focused on variation in the 3'-half of the gene, including the differentially spliced exons 9, 17, and 18, which have potential functional significance for the receptor. There was evidence of association to alcohol dependence for three *GRIK1* SNPs, particularly rs2832407 in intron 9) [95]. The only other kainate receptor gene that has been studied as a candidate for alcohol-related disorders is *GRIK3*, which encodes the GluR7 subunit. In a German case-control sample, Preuss et al. [96] found an association of a functional Ser310Ala polymorphism in *GRIK3* with a history of delirium tremens. That finding, however, was not replicated in Polish family-based or case-control samples, in which delirium tremens and other alcohol-related phenotypes, including alcohol dependence, were examined [97].

In addition to a potential role of *GRIK1* in determining the risk of alcohol dependence, this gene may have relevance for pharmacogenetic analysis. *GRIK1* was among the genes that were nominally associated with successful attempts to quit smoking in pooled genomewide association analyses in at least two of three independent treatment samples [98], supporting its potential utility as a moderator of treatment response in addictive disorders. This hypothesis was tested in a subgroup of individuals from a double-blind, study of heavy drinkers who were randomly assigned to treatment with topiramate 200 mg/day, topiramate 300 mg/day, or placebo) [99]. The medication was titrated to the target dosage over a 32-day period and then maintained at that dosage for one week. The frequency of heavy drinking was significantly lower in both topiramate groups compared to placebo. In 51 of the participants in this trial, Ray et al. [100] examined the three SNPs in *GRIK1* that had previously been nominally associated with alcohol dependence [95] as potential moderators of topiramate effects. Although there was no evidence that any of the SNPs moderated the therapeutic response to topiramate, the intron 9 SNP (rs2832407) was associated with the severity of topiramate-induced side effects and with serum levels of topiramate. Because topiramate's utility in the treatment of alcohol dependence is limited by its substantial adverse event burden [91], this finding, if replicated, could have important implications for the use of this medication.

Summary—Glutamate plays an important role in the risk for alcohol dependence and its pharmacologic treatment (as evidenced by the efficacy of acamprosate and topiramate). Using evidence of association to alcohol dependence risk, variation in *GRIK1*, which encodes a subunit of the kainate receptor that selectively binds topiramate, was found to moderate adverse effects associated with topiramate treatment. These findings, which potentially have important clinical implications, require replication. Careful examination of the pharmacogenetic effects of other glutamatergic genes may also yield important candidate variants for use in matching alcohol-dependent patients to treatment.

Conclusions

Converging developments in the treatment of alcoholism and in the genetics of alcohol dependence have begun to provide a basis for matching alcohol treatments to patients depending upon their genotype. However, study samples thus far have generally been small, and there are still conflicting results. To date, the most clinically relevant observation is that the presence of an Asp40 allele in a polymorphism in exon 1 of *OPRM1*, which encodes the μ-opioid receptor protein, modestly predicts a better response to naltrexone treatment. Other promising areas of investigation include the use of polymorphisms in *GABRA2* to predict response to specific psychotherapies and in *GRIK1* to predict adverse events resulting from topiramate treatment. These findings require replication in much larger samples and efforts to elucidate the mechanisms of their effects. Variation in many other genes has been associated with risk for alcohol dependence. Although some of these findings have been replicated, none have been studied as moderators of treatment effects. We recommend that, whenever possible, treatment trials include the collection of DNA samples to allow a much broader and more comprehensive analysis of pharmacogenetics. We also recommend that the genetic analyses be broadened to encompass more of the variation within more genes in the relevant systems; given our current state of knowledge and the complexity of the disease, it is too early to focus on a single variant in a single gene. Because there is a risk of inflating type 1 error through multiple comparisons, positive findings will require validation in multiple independent study samples. This, in turn, puts a premium on standardized study designs and methods, to maximize the comparability of findings from different studies.

A key impediment to the development of personalized medicine remains the business model that has driven much of the growth and maintenance of the pharmaceutical industry: viz. the development of “blockbuster” medications, sales of which generally exceed one billion dollars annually. To be so successful, such medications are marketed to large portions of the population, irrespective of individuals’ features, including genotype, which may moderate the therapeutic response or adverse effects associated with a particular medication. In the context of this business model, there has been little incentive for industry to identify patient characteristics that could be used to target medications to the individuals for whom they would have most benefit, because that could limit the size of their potential markets. However, as industry comes to recognize that there is a paucity of novel candidate medications that can be expected to achieve “blockbuster” status, medications development efforts may shift toward personalized medicine, to enhance the process by reducing cost by reducing the sample sizes required to demonstrate efficacy and the risk of adverse effects that can derail a candidate medication. A shift from the wholesale approach to medications development is likely to improve treatment of a wide variety of disorders, including alcohol dependence. Related to this, the current efforts to evaluate the efficacy of treatments and develop practice guidelines need to be sensitive to the genetic differences among individuals, since “one size will not fit all.”

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ABBREVIATIONS

AD	Alcohol-dependent patients
EA	European-American
GABA	γ-aminobutyric acid
HPA axis	hypothalamic-pituitary-adrenal axis
NAc	nucleus accumbens
NTSHD	Non-treatment-seeking heavy drinkers
SNP	single nucleotide polymorphism
VNTR	variable number of tandem repeats
VTA	ventral tegmental area

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Table 1

Studies of the *OPRM1* Asn40Asp Polymorphism as a Moderator of the Effects of Opioid Antagonists on Drinking Behavior

Authors (reference #)	Study Sample	Findings
Oslin et al. [41]	130 (AD, EA)	In patients with the Asp40 allele, naltrexone treatment resulted in significantly lower risk of relapse to heavy drinking than placebo treatment. No moderating effect on risk of any drinking. Asn40 homozygotes showed no medication effect.
Gelernter et al. [39]	215 (AD, EA, all male)	No moderating effect of the Asn40Asp polymorphism (or other polymorphisms in *OPRM1, OPRD1, OPRK1*) on naltrexone response, measured using a variety of drinking outcomes.
Anton et al. [41]	297 (AD, EA)	In patients with the Asp40 allele, naltrexone-treated patients had a significantly lower percentage of heavy drinking days and better global measure of treatment outcome than those on placebo. Asn40 homozygotes showed no medication effect.
Kim et al. [45]	63 (AD, Korean)	All patients received naltrexone treatment. Of the 32 treatment-adherent patients, carriers of the Asp40 allele took longer to relapse to heavy drinking.
Mitchell et al. [46]	30 (NTSHD, EA)	No moderating effect of the Asp40 allele in a brief, placebo-controlled trial of naltrexone.
Tidey et al. [47]	173 (NTSHD, 92% EA)	No moderating effect of the Asp40 allele on any drinking outcome in a brief, placebo-controlled trial of naltrexone.
Arias et al. [45]	272 (AD, Finnish)	No moderating effect of the Asn40Asp polymorphism (or other polymorphisms in *OPRM1, OPRD1, OPRK1*) on nalmefene response, measured using a variety of drinking outcomes.

AD, Alcohol-dependent patients; EA, European American; NTSHD, Non-treatment-seeking heavy drinkers