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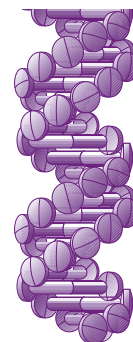
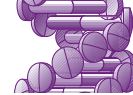
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Subjective response as a consideration in the pharmacogenetics of alcoholism treatment

Currently available pharmacological treatments for alcoholism have modest efficacy and high individual variability in treatment outcomes, both of which have been partially attributed to genetic factors. One path to reducing the variability and improving the efficacy associated with these pharmacotherapies may be to identify overlapping genetic contributions to individual differences in both subjective responses to alcohol and alcoholism pharmacotherapy outcomes. As acute subjective response to alcohol is highly predictive of future alcohol related problems, identifying such shared genetic mechanisms may inform the development of personalized treatments that can effectively target converging pathophysiological mechanisms that convey risk for alcoholism. The focus of this review is to revisit the association between subjective response to alcohol and the etiology of alcoholism while also describing genetic contributions to this relationship, discuss potential pharmacogenetic approaches to target subjective response to alcohol in order to improve the treatment of alcoholism and examine conceptual and methodological issues associated with these topics, and outline future approaches to overcome these challenges.

Keywords: 5-HT3 • 5-HTT • alcohol • alcoholism • GABAA • naltrexone • OPRM1 • pharmacogenetics • pharmacotherapy • subjective response

Overview

Alcoholism is a complex psychiatric disorder marked by the interplay between genetic and environmental risk factors [1]. A multitude of neurobiological and psychosocial pathways may lead to the outcome of heavy drinking, which may in turn result in the development of alcoholism. These intraindividual risk pathways include impulsive decision-making, externalizing psychopathology, and motivation to alleviate negative mood and/or anxiety symptoms. Another risk pathway for alcoholism is indexed by the acute subjective response to alcohol (SR) [2]. The subjective effects of alcohol involve both stimulant and sedative properties with the former being more prominent during the ascending limb of the blood alcohol concentration (BAC) curve and the latter being most salient during the descending limb [3–6]. Therefore, SR represents the interplay between both pleasurable and aversive effects [7], which over the course of repeated alcohol exposure will function as a determinant of future alcohol intake and related alcoholism risk.

The degree to which an individual experiences the stimulant and sedative acute effects of alcohol across the BAC curve may separately index future alcoholism risk. Individuals that demonstrate greater sensitivity to the stimulatory and rewarding effects (e.g., pleasurable/hedonic effects) of alcohol during the rising BAC limb are more likely to participate in binge drinking behavior and develop alcohol-related problems [3,8]. Furthermore, individuals who are less sensitive to the aversive effects of alcohol (i.e., sedative and unpleasant effects), particularly during the declining BAC limb, are also more likely to develop alcoholism [9–11]. Because SR represents a fairly discrete pathway of vulnerability to alcoholism, drugs that affect SR, either by

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attenuating alcohol's rewarding effects or increasing its aversive effects, have been targeted during medication development for alcoholism [2,12].

Currently approved pharmacological treatments for alcoholism in the USA have modest efficacy and high individual variability in treatment outcomes, both of which have been partially attributed to genetic factors [13–17]. One path to reducing this variability and improving the efficacy associated with these pharmacotherapies may be to identify shared genetic contributions to individual differences in both SR and alcoholism pharmacotherapy outcomes. Doing so may inform the development of personalized treatments that can effectively target converging pathophysiological mechanisms that convey risk for alcoholism. To that end, the objective of this review is threefold. First, it will review the well-established relationship between SR and the etiology of alcoholism, while also outlining recent findings of genetic associations to SR. Second, it will discuss potential pharmacogenetic approaches to target SR in order to improve the treatment of alcoholism. Finally, it will examine conceptual and methodological issues associated with pharmacogenetic considerations in the treatment of alcoholism and outline future approaches to overcome these challenges.

Subjective response to alcohol & alcoholism etiology

The acute pharmacological and subjective effects of alcohol are biphasic in nature [4,6,18]. Pharmacological effects refer to the cellular and physiological effects of alcohol while subjective effects describe an individual's self-reported perceptions of the substance's pharmacological effects. It has been well documented that when BAC is rising or reaches a stable peak, alcohol produces robust stimulatory and pleasurable subjective effects [3,5]. Conversely, alcohol's subjective effects are largely sedative and unpleasant as BAC declines [7]. While this pattern of SR has been well characterized across studies, individuals widely vary in their subjective experience of the pharmacological effects of alcohol: some individuals may be more or less sensitive to the rewarding and stimulant effects of alcohol, while others report variable sensitivity to alcohol's aversive and sedative effects. Alcohol administration studies have documented this variability in SR and have shown that these differences may play a significant role in predicting the frequency and quantity of alcohol use, as well as future alcoholism risk. When SR is divided into stimulant/rewarding and sedative/aversive effects, laboratory studies demonstrated that greater alcohol-induced stimulation and reward is associated with increased alcohol preference and consumption [19,20], whereas greater subjective experiences of the sedative

and unpleasant effects of alcohol, or reduced stimulation and reinforcement, are associated with decreased alcohol use and preference [21,22].

Schuckit and colleagues produced much of the early seminal work on both the assessment of SR during laboratory alcohol administration sessions and how SR may relate to future alcohol-related problems [23,24]. In these studies, the primary measure of SR was the Subjective High Assessment Scale (SHAS), which consists of various positive and negative mood-related adjectives, as well as a single item *ad hoc* scale of 'feeling high.' Principal components analysis of the SHAS suggested that the 'maximum terrible feelings' construct loaded into a first factor and accounted for 46% of the total variance [25,26], thereby suggesting that the SHAS may be most sensitive to the aversive effects of alcohol. In support, a factor analysis found that the SHAS is most strongly correlated with measures of alcohol-induced sedation [7]. A longitudinal study of sons of alcohol dependent probands and controls indicated that individuals who reported reduced sedative or aversive SR in the laboratory (measured by the SHAS) were more likely to develop alcoholism at follow-up [10]. While this is compelling evidence that SR predicts future alcohol-related problems, it is currently unclear how a reduced SR actually translates to real-world drinking behavior and conveys future alcoholism risk. It has been hypothesized that experiencing a reduced SR will lead to excessive alcohol consumption because these individuals will need to drink more to experience the effects of alcohol (Low Level of Response Model) [27], but as discussed by others [28,29] this theory remains untested.

An important effort toward resolving discrepancies in the alcohol administration literature comes from the work of Newlin and Thomson [25]. In the context of their review of alcohol challenge studies of sons of alcohol dependent parents and controls, they proposed the Differentiator Model for understanding psychobiological responses to alcohol as a function of family history of alcoholism. This model proposes that responses to alcohol may be accentuated during rising BAC (i.e., acute sensitization) and attenuated during falling BAC (i.e., acute tolerance). The authors propose that sons of alcohol dependent individuals may be at risk for alcoholism because they display both heightened sensitivity to the rewarding effects of alcohol during the rising limb of the BAC and reduced sensitivity to the unpleasant effects of alcohol as BAC declines. Acute tolerance and acute sensitization occur within session and represent a useful way to capture the 'snap shot' of alcohol's effects obtained in a single administration session. As most of the earlier studies by Schuckit and colleagues did not measure stimula-

tory responses to alcohol, this model has influenced efforts to parse out the SR phenotype into rewarding (primarily during the rising limb of BAC) and aversive dimensions (most salient during the descending limb of BAC). Accordingly, subjective scales, such as the Biphasic Alcohol Effects Scale [4], have been developed to directly assess the stimulant and sedative aspects of intoxication in alcohol administration studies.

Recent studies have provided support for the Differentiator Model by demonstrating that in heavy drinkers, compared with light drinkers, alcohol produces greater stimulatory and rewarding effects during the rising BAC limb and reduced sedative responses during the declining BAC limb [3,5]. Importantly, the heightened stimulatory and rewarding effects and decreased sedative responses were predictive of future increases in binge drinking behavior and the number of reported alcoholism symptoms [3,8]. Other similar findings have been reported, with stimulatory SR positively predicting both within-session and future real-world alcohol consumption [19,30–32]. These findings are somewhat consistent with the psychomotor stimulant theory of addictions which posits that the stimulatory and rewarding effects of addictive substances, including alcohol, share a common underlying biological mechanism and that individuals who experience greater alcohol-induced reward are thought to be more likely to develop alcoholism [33].

A recent meta-analysis [29] contrasting predictions from the Low Level of Response Model [10] and the Differentiator Model [25] found support for both models and argued that they describe two sets of distinct phenotypic risk, each with different etiological implications for alcoholism. In fact, the field is moving toward a paradigm shift in understanding SR as a pathway of risk. Specifically, there is increasing recognition that the rewarding/hedonic and sedative/aversive effects underlying responses to alcohol may be distinct and subserved by specific brain regions, neurotransmitters and functional circuitry. Further, it has been recommended that SR be specified by the response being measured, the amount and rate of alcohol administered, BAC, whether in the ascending or descending limb and the other potential risk factors under investigation [28]. Together, these recommendations are in line with the conceptualization of SR as a useful, yet complex, behavioral phenotype which challenges the field to reach more standard assessment methods and reporting conventions.

Genetics of the subjective response to alcohol

Genetic association studies typically rely on diagnostic phenotypes such as alcohol abuse or dependence, which are influenced by many different genetic as well

as environmental factors. Given the heterogeneity of diagnostic phenotypes, it has become increasingly important to identify more specific and narrowly defined behavioral phenotypes (i.e., intermediate phenotypes or ‘endophenotypes’) that are related to the larger disorder [34]. Endophenotypes are thought to facilitate research in the etiology and neurobiology of psychiatric disorders by being more homogenous and proximal to the underlying genetic variation than the broader, more heterogeneous diagnostic phenotype [34,35]. Importantly, SR is heritable [36,37] and, as we have previously reviewed [2], meets the specific criteria for an endophenotype [35]. Therefore, it may be advantageous to study the genetics of SR rather than the genotypes associated with a diagnostic phenotype, as endophenotypes like SR are presumed to be closer to the underlying neurobiology of alcoholism [2,38], such as biological mechanisms of alcohol-induced subjective reward (‘liking’) and craving (‘wanting’) [39].

There are multiple neurotransmitter systems underlying the subjective effects of alcohol [40]. Given the complexity of the neurobiological effects of alcohol, with different neurotransmitter systems being recruited at different ethanol doses and points of the BAC curve, we have argued that SR should be considered a moving target [41]. With that in mind, and due to evidence that genetic variation in particular neurotransmitter systems may affect both SR and alcoholism pharmacotherapy outcomes, we have selected three neurotransmitter systems to focus on for the remainder of the review: the endogenous opioid system, the GABAergic system and the serotonergic system.

The endogenous opioid system is involved with the acute pharmacological effects of alcohol, as alcohol administration results in the activation of opioid receptors in the ventral tegmental area and nucleus accumbens, which subsequently affects extracellular concentrations of dopamine in the mesolimbic pathway, thereby contributing to the motivational and reinforcing properties of alcohol [42–46]. Accordingly, multiple genetic association studies have examined whether allelic variation in *OPRM1* is related to various alcoholism-related phenotypes. In particular, a SNP of *OPRM1*, the Asn40Asp SNP (rs1799971) has received significant attention in candidate gene studies. Note that although this SNP is referred to in the literature, as well as this manuscript, as the Asn40Asp (or the A118G SNP), this designation has been recently updated in the public bioinformatics databases (ABI, NCBI, HapMap) as it has been determined that the mu-opioid receptor may contain an additional 62 amino acids. The new designation of this SNP on the NCBI Human Genome Assembly 36 is Asn102Asp (or A355G) [47].

This variant results in an amino acid change from asparagine to aspartic acid and eliminates a putative glycosylation site in the N-terminal extracellular loop of the receptor protein. Despite numerous examinations, the molecular consequences of this substitution remain unclear. The initial study that identified this variant reported it to modestly increase receptor binding affinity for β -endorphin, consistent with a straightforward gain-of-function role of the mutation [48]. Subsequent studies from the same group [49] and others [46,50] have, however, not replicated these findings. Furthermore, the minor allele at this locus (Asp40) has been associated with lower levels of receptor expression *in vitro* [50] and with reduced receptor binding potential in a recent positron emission tomography (PET) study [51], the latter of which may also indicate a decrease in the number of mu receptors. While numerous studies suggest that this variant is functional, there is conflicting evidence suggesting either a gain-of-function or a loss-of-function mutation depending on the experimental conditions. For instance, this variant was associated with reduced morphine potency, as measured by miosis in humans [52] and inhibition of intracellular Ca^{2+} currents in humanized mice [53], suggesting a loss-of-function. Yet, studies of alcohol effects presumably rely on the actions of endogenous opioid peptides released in response to alcohol and, as reviewed below, many alcohol administration studies suggested the minor allele to be a gain-of-function variant.

Several human laboratory studies have examined the effect of the Asn40Asp SNP on SR, with mixed results. A series of studies have shown that compared with Asn40 homozygotes, Asp40 carriers have reported greater subjective stimulation, reward and positive mood after IV alcohol administration in the laboratory [54,55] and after alcohol consumption in the natural environment [30]. An interesting recent finding in an alcohol dependent sample suggested that a variable number of tandem repeats (VNTR; rs28363170) in *SLC6A3* may moderate the effects of the Asn40Asp SNP on SR, with Asp40 carriers who were also homozygous for the 10-repeat allele (A10) of *SLC6A3* reporting heightened alcohol-induced stimulation, vigor and positive mood [56]. These studies support the endogenous mu-opioid system as being functionally related to the hedonic effects of alcohol and suggest that the stimulatory and rewarding SR may be positively associated with the *OPRM1* Asn40Asp SNP.

Conversely, a subset of laboratory studies has reported null findings on the relationship between *OPRM1* and SR. One recent study in nontreatment-seeking alcohol dependent individuals found *OPRM1* Asn40 homozygotes self-reported more stimulation than Asp40 carriers, which is contrary to the results of prior stud-

ies [57]. In an IV alcohol self-administration paradigm in young, heavy drinkers, *OPRM1* Asp40 carriers and Asn40 homozygotes did not differ in their SR, yet minor allele carriers did self-administer substantially more alcohol and reach a higher BAC than individuals homozygous for the common allele [58]. Additionally, a study in American Indians indicated that Asp40 carriers, versus Asn40 homozygotes, reported expecting a more intense aversive SR (e.g., feeling terrible, sleepy, nausea, etc.), which was subsequently correlated with the diagnosis of an alcohol use disorder and lower levels of real-world alcohol use [59]. While these discrepant findings are difficult to explain, they may be related to several factors, such as using retrospective self-reports of expected SR instead of employing actual alcohol administration and measurement of acute SR, differences in sample ethnicities (e.g., Caucasian vs American Indians), or variability in participant drinking frequency/quantity and disorder severity (e.g., controls vs heavy drinkers vs alcohol dependent samples), the latter of which may serve as a proxy for the progressive stages of alcohol-related problems. This factor may be essential in detecting the effects of *OPRM1* on SR, as several prominent theories of addiction suggest that the hedonic effects of alcohol are most salient in the early stages of alcoholism (e.g., the transition from alcohol abuse to dependence), whereas alcohol consumption in late stage alcoholism is primarily driven by negative reinforcement processes [43,60]. Thus, as the endogenous opioid system may be predominantly related to the hedonic or stimulatory effects of alcohol, the effects of the *OPRM1* Asn40Asp SNP on SR may be most evident in individuals who are still in the early stages of alcoholism. While recent human laboratory studies have provided some initial support for these notions of SR transition across stages of alcoholism [54,61], more research in both at-risk and dependent populations is needed to characterize the transition in SR from positive to negative reinforcement and how *OPRM1* genotype may contribute to this progression. On balance, the *OPRM1* Asn40Asp SNP has been implicated in SR, particularly sensitivity to the stimulatory and rewarding effects of alcohol. Yet, the effects of other opioid receptor genes on alcohol response have not yet been characterized despite plentiful evidence in rodents suggesting that both kappa and delta opioid receptors are involved alcohol self-administration and acute alcohol response [62–66].

While *OPRM1* may be involved in the stimulatory and rewarding SR, genetic markers underlying the sedative SR have not been as well characterized. Exploratory genetic association studies have examined candidate genes for reduced sensitivity to the sedative effects of alcohol and provided modest support for the

role of genetic variation in the GABAergic and serotonergic systems in this SR [67–69]. Both the rewarding and sedative effects of alcohol, more prominent during the ascending and descending BAC limbs, respectively, may in part be mediated by γ -aminobutyric acid (GABA) neurotransmission [40,70–72]. The GABA_A receptor is one of alcohol's few primary targets and can directly modulate alcohol's effects on the mesolimbic dopamine system [40]. Thus, variation in genes encoding GABA_A receptors may play an important role in the SR.

Genes coding for the GABA_A receptor and its subunits have been associated with SR, particularly with regard to its sedative or aversive effects. Specifically, several alcohol administration studies have examined variation in two chromosome 4p genes that code for the α -2 and γ -1 subunits of the GABA_A receptor: *GABRA2* and *GABRG1*, respectively. Several *GABRA2* variants were associated with reduced negative/aversive SR after oral alcohol dosing, particularly during the declining BAC limb [73], attenuated levels of subjective high and intoxication during IV administration [74,75] and lower hedonically rewarding SR during the ascending BAC limb after oral administration [76]. Furthermore, a study of subclinical heavy drinkers found that a SNP of the *GABRG1* gene (rs1497571) was associated with retrospective reports of attenuated levels of alcohol intoxication [77]. Importantly, while no functional variants have been found for either *GABRA2* or *GABRG1*, and the underlying mechanistic changes related to alcohol responsivity are currently unclear, markers in the 5'-region of *GABRG1* are in linkage disequilibrium with markers in the proximal *GABRA2* [78,79]. Although results have not been unanimous [80], these preliminary studies highlight the potential importance of genetic variation in GABA_A receptor subunit genes to the sedative and aversive effects of alcohol.

Genetic variation in the serotonergic system may also be involved with the sedative SR. Like the GABA_A receptor, the serotonin 5-HT₃ receptor is another primary target of alcohol that can modulate mesolimbic dopamine activity, potentially through alcohol-induced potentiation of its function [81–84]. The serotonin transporter (5-HTT) is encoded by *SLC6A4* and plays an essential role in serotonergic neurotransmission and 5-HT₃ receptor activity. A common polymorphism (5-HTTLPR) in the VNTR in the promoter region of *SLC6A4* is associated with altered 5-HTT activity, cumulating in changes in synaptic serotonin levels and clearance rates [85,86]. While to date 5-HT₃ variants have not been examined in relation to SR, the high activity 5-HTTLPR polymorphism was associated with reduced sedation (as measured by the SHAS) after acute oral alcohol administration [69,87] and lower

retrospective self-reports of intoxication levels during drinking episodes [88]. Next we discuss how genetic associations with SR may be applied to treatment development and pharmacogenetics in particular.

Subjective response to alcohol & alcoholism treatment

Due to the previously described relationship with alcoholism etiology, SR has been studied in the laboratory as a potential therapeutic target of medication development for alcoholism [38]. Several studies have suggested that naltrexone, an opioid receptor antagonist, exerts its clinical effects in part by blocking the positively reinforcing effects of alcohol and also by increasing its aversive effects. Specifically, naltrexone alters SR by dampening reports of stimulation [89–91] and 'high,' [92] decreasing ratings of liking and enjoyment of alcohol's effects [90,93], and increasing self-reported fatigue, tension and confusion [94]. Other potential alcoholism pharmacotherapies may similarly attenuate alcohol-induced reward or potentiate its aversive effects. For example, a pilot study of quetiapine in alcohol dependent individuals found that it reduced subjective intoxication and, in particular, alcohol-induced sedation during alcohol administration [95]. Further, a study of varenicline, a partial nicotinic receptor agonist, found that it potentiated the negative and dysphoric subjective effects of alcohol [96]. Together, these studies highlight the potential clinical utility of assessing SR as a treatment target for alcoholism. Specifically, some effective medications for alcoholism may reduce motivation to drink by 'blocking the buzz' [60,97], or in other words, attenuating the positively reinforcing effects of alcohol. Other medications may work by potentiating the aversive and sedative effects of alcohol, or attenuating negative affective states that ultimately emerge in the absence of alcohol. As highlighted by Litten and colleagues [98], there are many promising medications with numerous pharmacological targets being examined as potential alcoholism treatments. Yet, the effects of the majority of these potential pharmacotherapies on SR have not been tested in the laboratory, leaving the biobehavioral mechanisms of action for these medications unknown.

Pharmacogenetics of alcoholism treatment

Many currently approved and potential medications for alcoholism pharmacotherapy target the same neurotransmitter systems that are also involved with SR. Thus, it is plausible that genetic variants that contribute to SR may also affect medication efficacy. For example, although naltrexone is not entirely selective for any of the opioid receptor subtypes, the mu-opioid receptor subtype encoded by *OPRM1* is thought to be its primary target at clinically used doses. Given that

naltrexone attenuates alcohol-induced reinforcement and that the *OPRM1* Asn40Asp SNP is associated with the rewarding SR, it stands to reason that individuals with the Asp40 allele may have altered responsivity to the behavioral and clinical effects of naltrexone. The following section will discuss results of studies that examined whether genetic variants that have previously been associated with SR, namely variants of *OPRM1*, GABA_A receptor genes, and the serotonergic system, may also be promising pharmacogenetic targets for alcoholism treatment (summarized in Table 1).

OPRM1 & naltrexone: laboratory studies

Several laboratory pharmacogenetic studies have provided support for a functional relationship between the Asn40Asp SNP and response to naltrexone. One such study in heavy drinkers found that Asp40 carriers, versus Asn40 homozygotes, reported greater naltrexone-induced blunting of alcohol 'high,' which may provide a biobehavioral mechanism by which naltrexone may be differentially effective among minor allele carriers [90]. As previously discussed, individuals who carry the Asp40 allele may demonstrate a greater rewarding SR and, because of this predisposition, may also be more sensitive to naltrexone's ability to dampen alcohol 'high.' A recent study has provided partial support for this notion, as naltrexone blunted alcohol 'euphoria' in Asp40 carriers in a sample of social drinkers [99]. However, this effect was only observed in women and did not extend to a progressive ratio paradigm, as naltrexone did not attenuate motivation to work for additional alcoholic beverages. Interestingly, another study in heavy drinkers found that the relationship between alcohol craving and alcohol consumption was greater in Asp40 carriers than Asn40 homozygotes; yet, naltrexone was able to effectively negate this potentially problematic relationship in Asp40 carriers than Asn40 homozygotes, which again suggests that minor allele carriers may be more sensitive to naltrexone's effects [100]. Finally, a placebo-controlled laboratory study of naltrexone among heavy drinkers of East Asian descent (i.e., Chinese, Korean or Japanese) found that Asp40 carriers experienced greater alcohol-induced sedation, subjective intoxication and lower alcohol craving when on naltrexone than Asn40 homozygotes [101]. These findings extend previous studies of naltrexone pharmacogenetics to individuals of East Asian descent, an ethnic group more likely to carry the minor allele putatively associated with improved biobehavioral and clinical response to this medication [101]. In sum, the results of these laboratory studies of naltrexone pharmacogenetics suggested that those who may be most sensitive to alcohol-induced reward and -related craving (i.e., Asp40 carriers), and thereby

potentially at greatest risk for alcoholism, may also be the most responsive to naltrexone pharmacotherapy.

However, the results from other laboratory studies of naltrexone have not supported this theorized role for the Asn40Asp SNP. In a sample of nontreatment-seeking heavy drinkers, naltrexone produced greater cue-induced craving in Asp40 carriers than Asn40 homozygotes in the laboratory [102] and had no pharmacogenetic effect on alcohol consumption and urge to drink in the natural environment [103]. Similarly, no pharmacogenetic effect of naltrexone on alcohol cue-reactivity measures was found in a mixed sample comprised of both nontreatment-seeking and treatment-seeking alcohol dependent individuals [104]. Finally, a small neuroimaging study did not find an interactive effect of the *OPRM1* Asn40Asp SNP and naltrexone on behavioral outcomes or neural response during a delay discounting task [105].

OPRM1 & naltrexone: clinical trials

The impact of the Asn40Asp SNP on naltrexone's efficacy on drinking outcomes during alcohol clinical trials has also been thoroughly investigated. A combined reanalysis of three separate clinical trials found that naltrexone was more effective in reducing relapse rates and increasing the time to first heavy-drinking day in individuals with at least one copy of the Asp40 allele, as compared with Asn40 homozygotes [106]. In fact, Asp40 carriers were the only ones to benefit from naltrexone, while no difference between naltrexone and placebo was observed in subjects homozygous for the major Asn40 allele. In the Combining Medications and Behavioral Interventions for Alcoholism (COMBINE) Study, which was a large multisite trial that was well-powered to retrospectively examine potential pharmacogenetic effects, it was found that naltrexone plus Medication Management (MM; a minimal form of behavioral intervention) significantly decreased heavy-drinking days to a greater extent in Asp40 carriers than Asn40 homozygotes. A total of 87% of carriers of the Asp40 allele were classified as having a good clinical outcome to naltrexone plus MM, while only 55% of Asn40 homozygotes were similarly classified, suggesting a clinically meaningful role for the Asn40Asp SNP [107]. These findings were supported in haplotype-based reanalyses of the COMBINE Study data set, which found that the Asn40Asp SNP was the sole *OPRM1* locus that was predictive of the good clinical outcome to naltrexone [108]. Finally, in a recent meta-analysis of six clinical trials that reported the relationship of the Asn40Asp SNP with naltrexone's efficacy on drinking outcomes in alcohol dependent patients, it was found that naltrexone-treated individuals carrying the Asp40 allele had lower relapse rates than Asn40 homozygotes [109].

Table 1. Pharmacogenetics of alcoholism treatment summary.

Gene and medication	Population	Findings	Ref.
<i>OPRM1</i> (rs1799971) & naltrexone: laboratory studies			
	HD	+ Naltrexone blunted of alcohol 'high' to a greater extent in Asp40 carriers vs Asn40 homozygotes	[90]
	Social drinkers	+ Naltrexone blunted alcohol 'euphoria' in female Asp40 carriers	[99]
		- No pharmacogenetic effect of Asn40Asp and naltrexone on motivation to work for alcoholic beverages	
	HD	+ Naltrexone reduced the relationship between craving and alcohol consumption in the natural environment in Asp40 carriers but not Asn40 homozygotes	[100]
	HD (East Asian descent)	+ Naltrexone produced greater alcohol-induced sedation, subjective intoxication and lower alcohol craving in Asp40 carriers than Asn40 homozygotes	[101]
	HD	- Naltrexone produced greater cue-induced craving in Asp40 carriers than Asn40 homozygotes in the laboratory	[102]
	HD	- No pharmacogenetic effect of Asn40Asp and naltrexone on alcohol consumption and urge to drink in the natural environment	[103]
	AD (treatment- + nontreatment-seeking)	- No pharmacogenetic effect of Asn40Asp and naltrexone on cue-reactivity measures	[104]
	AD (unclear if treatment-seeking), healthy controls	- No pharmacogenetic effect of Asn40Asp and naltrexone on behavioral outcomes or neural response to a delay discounting task	[105]
<i>OPRM1, SLC6A3</i>	AD (nontreatment-seeking)	- No pharmacogenetic effect of Asn40Asp alone and naltrexone on reducing drinking behavior	[57]
		+ Naltrexone decreased alcohol consumption in the natural environment in Asn40 homozygotes with at least one DAT1 9 VNTR (rs28363170)	
<i>OPRM1</i> (rs1799971) & naltrexone: clinical trials			
	AD	+ In a reanalysis of three separate clinical trials, naltrexone was more effective in reducing relapse rates and increasing the time to first heavy-drinking day in Asp40 carriers than Asn40 homozygotes	[106]
	AD	+ Naltrexone plus therapy decreased heavy-drinking days to a greater extent in Asp40 carriers than Asn40 homozygotes	[107]
	AD	+ Haplotype-based reanalyses of [107] found that the Asn40Asp SNP was the sole <i>OPRM1</i> locus predictive of 'good clinical outcome' to naltrexone	[108]
	AD	+ Meta-analysis of six clinical trials of naltrexone and <i>OPRM1</i> pharmacogenetics found that naltrexone-treated Asp40 carriers had lower relapse rates than Asn40 homozygotes	[109]
	AD	- No pharmacogenetic effect of Asn40Asp and naltrexone on relapse to heavy drinking	[110]
	AD	- No pharmacogenetic effect of Asn40Asp and naltrexone on reduction in drinking or alcohol craving	[111]
	AD (Korean descent)	+ Naltrexone decreased relapse rates in Asp40 carriers compared with Asn40 homozygotes	[112]
AD: Alcohol dependent individuals, treatment seeking unless otherwise noted; HD: Heavy drinkers, nontreatment-seeking unless noted.			

Table 1. Pharmacogenetics of alcoholism treatment summary (cont.).

Gene and medication	Population	Findings	Ref.
Other potential pharmacogenetic targets			
Naltrexone			
<i>OPRK1, OPRD1</i>	HD	+ <i>OPRK1</i> (rs997917): naltrexone produced greater naltrexone-induced sedation in C allele carriers than TT homozygotes + <i>OPRD1</i> (rs4654327): Naltrexone blunted alcohol stimulation and craving to a greater extent in A allele carriers vs GG homozygotes	[113]
Topiramate			
<i>GRIK1</i>	HD (treatment-seeking)	+ <i>GRIK1</i> (rs2832407): topiramate reduced heavy-drinking days to a greater extent than placebo in C allele homozygotes than A allele carriers	[114]
<i>GRIK1</i>	HD	+ <i>GRIK1</i> (rs2832407): Topiramate produced less severe side effects in C allele homozygotes than A allele carriers	[115]
Ondansetron			
<i>SLC6A4</i>	AD	+ Ondansetron reduced drinking behavior and increased abstinence rates in individuals homozygous for the high activity 5-HTTLPR polymorphism vs low activity variants	[116]
<i>SLC6A4</i>	AD (nontreatment-seeking)	+ Ondansetron reduced drinking behavior in the natural environment and alcohol self-administration in the laboratory in individuals homozygous for the high activity 5-HTTLPR polymorphism vs low activity variants	[117]
<i>SLC6A4, 5-HT3</i>	AD	+ Reanalyses of [116] suggested ondansetron was more effective in reducing heavy-drinking days if individuals carried one or more of several 5-HT3 SNPs (rs1176713, rs1150226, rs17614942), which was further enhanced in combination with the high activity 5-HTTLPR polymorphism	[118]

AD: Alcohol dependent individuals, treatment seeking unless otherwise noted; HD: Heavy drinkers, nontreatment-seeking unless noted.

Similarly to laboratory studies of *OPRM1* and naltrexone, pharmacogenetic clinical trials of naltrexone and *OPRM1* have also produced mixed results. A clinical trial in male veterans did not demonstrate an effect of Asn40Asp on clinical response to naltrexone [110], nor did a smaller trial in a mixed alcohol dependent sample [111]. Another study in nontreatment-seeking alcohol dependent individuals did not find an effect of Asn40Asp alone on naltrexone's efficacy on reducing drinking behavior but did report a promising genetic interaction between this SNP and the *SLC6A3* VNTR (rs28363170) polymorphism on naltrexone responsiveness [57]. In the previously mentioned COMBINE Study, there was neither a discernible effect of naltrexone nor an *OPRM1* pharmacogenetic interaction in individuals who received an extensive psychosocial intervention, suggesting that robust psychotherapy can obscure pure pharmacological, as well as pharmacogenetic effects. An additional factor that almost certainly contributes to these mixed findings is that the effect size of this or any pharmacogenetic interaction is

relatively small. It is commonly accepted that multiple genes of small effect sizes contribute to the development of most psychiatric disorders [119]. As it is likely that alcoholism and drug addictions adhere to a similar polygenic framework as other psychiatric disorders, it is plausible that the Asn40Asp SNP contributes a relatively small effect size for this particular pharmacogenetic interaction with naltrexone, which in turn can account for the mixed findings. Such null findings highlight the need to cautiously evaluate all empirical evidence before pharmacogenetic prescriptions can be made regarding naltrexone for alcoholism. As highlighted by Gelernter and colleagues [110], attention to additional opioid genes such as those encoding kappa (*OPRK1*) and delta receptors (*OPRD1*), which are also targeted by naltrexone, represents an important avenue for future research. In fact, a recent study indicated that *OPRK1* and *OPRD1* SNPs might contribute to naltrexone's amplification of alcohol-induced sedation and blunting of alcohol-related stimulation, respectively [113].

As the Asp40 minor allele frequency is imbalanced across ethnic groups [101], studies have examined whether the previous findings from naltrexone clinical trials in predominantly Caucasian samples could be extended to other ethnicities. For example, in a sample of Korean alcohol dependent patients who adhered to treatment, naltrexone improved relapse rates in Asp40 carriers compared with Asn40 homozygotes [112]. As with the results of the laboratory studies discussed above, there is evidence that this polymorphism may be stratified by sex. The Asp40 allele was found to be overrepresented in Korean women with alcohol dependence, but not men [120]. This may be relevant to treatment with naltrexone, as some clinical trials have reported men demonstrate better outcomes to naltrexone pharmacotherapy [121,122], although these reported differences may be due to power limitations and/or the selected outcome measures [123]. Of note, the COMBINE Study data set was reanalyzed to examine the efficacy of naltrexone in solely African American participants [124]. In contrast to the overall sample, naltrexone did not display efficacy in this ethnic group. It was speculated that the lack of naltrexone effect might be explained by the low Asp40 allele frequency among African Americans (~7% in the COMBINE Study). While it remains unclear how *OPRM1* may contribute to naltrexone responsiveness in alcohol dependent African Americans, there are pharmacogenetic trials currently underway examining the Asn40Asp SNP in Asian Americans (NCT02026011). Ancestry and ethnicity specific effects remain a critical area of investigation for pharmacogenetic addiction studies. Population effects and allele frequency considerations may become of particular importance as the field of pharmacogenetics (and genomics) progresses, as these issues may have implications for health disparities in the era of personalized medicine [125].

OPRM1 & naltrexone: summary

In summary, results from laboratory studies and clinical trials provide some evidence that the Asn40Asp SNP is associated with a differential SR and is a predictor of the clinical response to naltrexone, the latter of which is supported by a recent meta-analysis [109]. Yet, due to negative or inconclusive results from a sizable number of pharmacogenetic studies, these findings have been met with a healthy level of skepticism and substantial work remains to be done before the promise of targeted therapies may be realized for naltrexone. Nevertheless, the relationship between naltrexone and the *OPRM1* Asn40Asp SNP is still promising, and further research is needed to elucidate the biological and clinical plausibility of related pharmacogenetic approaches. A large, prospective pharmacogenetic trial of naltrexone that is currently underway at the University of Pennsylvania [126] will hopefully provide further clarification on the clinical utility of *OPRM1*.

Other pharmacogenetic targets

In contrast to the plentiful number *OPRM1* studies, few studies have examined whether the genes that contribute to the acute sedative or aversive response to alcohol (e.g., *GABRA2*, *GABRG1*, or *SLC6A4*) are also pharmacogenetic targets for alcoholism treatment. Unfortunately, no medications that have GABA_A receptors as a primary target are currently being tested clinically [98], although there are recent promising pre-clinical findings in nonhuman primates [127]. A recent meta-analysis of several clinical trials supported topiramate, which is thought to have action at GABA_A receptors as well as antagonist effects at AMPA and kainite glutamate receptors, as a promising pharmacological treatment for alcoholism [128]. However, little evidence has been reported on whether topiramate affects acute SR [129], and while a pharmacogenetic effect of a kainite receptor SNP on clinical response to topiramate

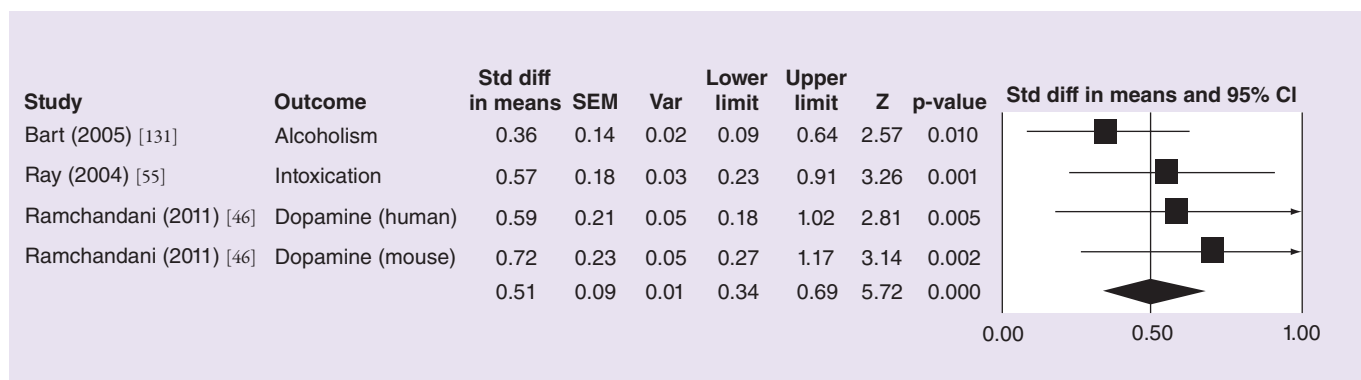


Figure 1. Effect size estimates for studies of the A118G SNP of *OPRM1* across alcoholism phenotypes. All studies reported significant genetic findings and in the same direction, such that Asp40 carriers scored higher than Asn40 homozygotes.

SEM: Standard error of the mean; Std diff: Standard difference; Var: Variance.

Reproduced with permission from [132].

was recently reported in two separate studies [114,115], the genetic contribution of GABA_A receptor variants to topiramate efficacy has yet to be examined. Thus, despite the preliminary evidence that variation in genes encoding subunits of the GABA_A receptor contributes to the sedative SR, it is presently unclear if this site is also a viable pharmacogenetic target for alcoholism treatment.

Conversely, recent work examining the efficacy of ondansetron, a 5-HT₃ receptor antagonist that is FDA approved for treating chemotherapy-related nausea, as a potential alcoholism treatment has provided highly promising findings advocating the serotonergic system as a pharmacogenetic target. For example, in a recent clinical trial, individuals homozygous for the high activity 5-HTTLPR polymorphism, which was previously associated with attenuated sedative SR [69,87], showed greater reductions of drinking behavior and more days abstinent with ondansetron than individuals possessing a low activity variant [116]. Similar results were also presented in a smaller laboratory study in non-treatment-seeking alcohol dependent individuals [117]. Additionally, secondary analyses of the clinical trial described above [116] suggested an enhanced pharmacogenetic effect of the high activity 5-HTTLPR polymorphism when interactions with another *SLC6A4* SNP (rs1042173) [116] and several *5-HT3* SNPs were also considered [118]. While the neurobiological mechanisms underlying the relationship between *5-HT3* and *SLC6A4* variants and ondansetron treatment outcomes are currently unknown, these results implicate the serotonergic system, in particular the 5-HTTLPR genotype, as a potential pharmacogenetic target for alcoholism and again provide evidence that the same genetic variants that contribute to SR may also predict medication efficacy.

Future perspective & conclusion

As discussed in this manuscript and recently argued in factor-analytic [7], meta-analytic [29], review [2,130], and opinion papers [28], SR is a multidimensional construct that may underlie discrete risk pathways for development of alcohol-related problems. Although additional dimensions may be discovered by future studies, two distinct SR risk phenotypes have been well characterized in the literature and may each present unique treatment implications. The first SR risk pathway is predominantly distinguished by a greater sensitivity to the hedonic and stimulatory effects of alcohol, while the second is typified by an attenuated sensitivity to the aversive and sedative effects of alcohol. While individuals may experience different magnitudes of each SR due to a multitude of factors, genetic studies have offered some support that specific

neurotransmitter systems may be preferentially associated with either SR risk phenotype (e.g., opioidergic variants with the hedonic/stimulatory phenotype and GABAergic or serotonergic variants with sedative/aversive phenotype). Importantly, several genetic variants appear to be related both to a single SR phenotype and to pharmacological treatment outcomes, indicating that using pharmacogenetic approaches targeting SR may be a promising method to ultimately improve alcoholism treatment outcomes. However, several sizeable impediments remain before SR can be realized as a potential pharmacogenetic treatment target.

First, a reoccurring issue across genetic studies in all substance abuse related fields is lack of replication, which is partially related to the inherently small effect size contributed by any single genetic variant to the response to alcohol or to pharmacological treatments. Complicating this issue further is the likelihood that multiple genes of small effect sizes contribute to the development of psychiatric disorders, including alcoholism [119]. Because of these effect size-related issues, many have speculated that endophenotypes, such as SR or BOLD response to alcohol administration, may be closer to the underlying neurobiology of alcoholism and, therefore, increase the reliability of genetic studies by improving the statistical power to detect genetic effects over diagnostic phenotypes (i.e., diagnosis of alcohol dependence or alcohol use disorder). However, this issue is predominantly raised in theory and not addressed empirically. Thus, in order to illustrate whether SR and other endophenotypes do provide a meaningful increase in power over the diagnostic phenotype, we have examined the effect size estimates, which is a necessary requirement for power analysis, from four previously published alcohol-related studies that reported significant findings of the *OPRM1* Asn40Asp SNP (rs1799971) using different outcome variables.

The first study we examined is a traditional case-control association study that reported that *OPRM1* was related to the prevalence of the diagnostic phenotype of alcohol dependence in a Swedish sample [131], while the second is a human laboratory study that reported *OPRM1* was associated with the stimulant/rewarding SR in moderate/heavy drinkers [55]. The third and fourth studies, respectively, quantified striatal dopamine release in response to alcohol administration using PET imaging in social drinkers and microdialysis in humanized mice [46]. The effect size estimates, as presented in Figure 1, suggest that as we use measures that are closer to the neurobiology of alcohol response and further away from the diagnostic phenotype, statistical power to detect an effect does indeed increase. This is comparable to the analogy of ‘cranking up the

microscope' from a broad diagnostic phenotype to a behavioral and pharmacological phenotype (i.e., SR), then to a more neurobiologically based measure in humans, and ending in the controlled animal model. Interestingly, these effect size estimates suggest that SR and neuroimaging may provide equivalent gains in power over using diagnostic outcomes. As other laboratory studies have also reported analogous effect sizes between SR and objective alcohol response measures [5], SR may therefore offer a reliable and cost-effective alternative over neuroimaging when studying the effects of genotype on response to alcohol administration. However, future studies are clearly needed to

replicate and extend these findings by effectively quantifying the gain in statistical power related to a host of endophenotypes within a single sample.

While the SR endophenotype may offer a more powerful alternative to diagnostic phenotypes in identifying genetic effects, it still remains to be determined whether this endophenotype is a viable target for alcoholism pharmacotherapy. As reviewed earlier in this paper, reducing the pleasurable or increasing the aversive effects of alcohol is considered a marker of efficacy in the development of alcoholism medications in the laboratory. For example, naltrexone has been theorized to reduce the hedonically rewarding subjec-

Executive summary

Subjective response to alcohol & alcoholism etiology

- Individuals widely vary in their acute subjective response to alcohol (SR) and the directionality and degree of this response may confer risk for the development of alcoholism.
- Those who experience heightened stimulatory and rewarding SR during the rising limb of the blood alcohol concentration curve and/or reduced sedative/aversive SR during the declining limb of the blood alcohol concentration curve have increased risk for alcoholism development.

Genetics of the subjective response to alcohol

- A SNP of the mu-opioid receptor gene (*OPRM1*), the Asn40Asp SNP (rs1799971), may be involved in the positively reinforcing SR. Individuals who carry at least one copy of the Asp40 allele report greater alcohol-induced stimulation and reward than Asn40 homozygotes.
- Variants of genes encoding subunits of the GABA_A receptor and the serotonin transporter (5-HTT) may be related to the sedative/aversive SR. For example, a polymorphism (5-HTTLPR) in the gene that encodes the 5-HTT, *SLC6A4*, may be associated with reduced sedative SR.

Subjective response to alcohol & alcoholism treatment

- The SR has been studied in the laboratory as a therapeutic target of medications for alcoholism. Treatments that attenuate the positively reinforcing SR or potentiate the aversive/sedative SR are often viewed as potentially clinically useful.

Pharmacogenetics of alcoholism treatment

- Medications for the treatment of alcoholism, both those approved for current use and those still under development, often target the same neurotransmitter systems that are involved with SR. Therefore, genetic variants that contribute to the SR may also affect a medication's efficacy in treating alcoholism.
- Laboratory studies and clinical trials have provided evidence that the Asn40Asp SNP is predictive of response to naltrexone, with Asp40 allele carriers (vs Asn40 homozygotes) showing greater naltrexone-induced blunting of alcohol's rewarding effects and better treatment outcomes with naltrexone.
- The 5-HTTLPR polymorphism may be related to clinical response to ondansetron, as individuals homozygous for the high activity 5-HTTLPR polymorphism showed better treatment outcomes with ondansetron than individuals possessing a low activity variant.
- These pharmacogenetic studies provide evidence that the same genetic variants that contribute to SR, and potentially confer risk for alcoholism development, may also predict pharmacotherapy treatment outcomes.

Future perspective

- Effect size estimates indicate that as genetic association studies move away from using an alcoholism diagnostic phenotype and closer to the neurobiology underlying acute alcohol response, the statistical power to detect a genetic effect also increases (Figure 1). Laboratory studies measuring SR, neuroimaging studies measuring BOLD response to alcohol, and animal studies directly measuring neurotransmitter response to alcohol administration all offer a more powerful alternative to those using diagnostic phenotypes to detect genetic effects.
- It still remains to be determined whether SR is a viable target for alcoholism pharmacotherapy and pharmacogenetics, as it is currently unclear whether a medication's ability to alter SR is related to that medication's efficacy in a clinical trial setting. Additionally, before SR can be used as a target for pharmacogenetic treatment approaches, future studies need to clearly characterize how different genotypes relate to specific dimensions of SR as a function of alcohol dosage, limb of intoxication, risk factor under study and stage of alcoholism.

tive effects of alcohol, thus reducing the probability of a heavy-drinking event occurring [57]. However, to our knowledge, no study has explicitly examined whether a medication's ability to alter SR is predictive of the efficacy of that medication in a clinical trial setting. Confounding this limitation, current theories of addiction theorize that alcohol's positively reinforcing effects convey the greatest risk early in the transition from heavy-drinking to dependence, whereas late stage alcoholism is characterized primarily by negative reinforcement processes [43,60]. Therefore, a medication that targets one-dimension of SR (e.g., reducing the hedonic effects of alcohol) may only be clinically useful during a particular stage of alcoholism [54,61]. Before SR can be used as a tool to confidently identify potential pharmacogenetic targets for alcoholism treatment, future studies must first identify whether these responses are clinically meaningful markers of a medication's efficacy.

In conclusion, while SR may be a useful marker for identifying alcoholism risk and statistically powerful endophenotype for detecting genetic effects, it has only relatively recently been characterized as a multidimensional construct. Thus, it is still unclear how SR risk

phenotypes can be effectively translated into the treatment of alcoholism, both conceptually and practically. Furthermore, although several promising genetic variants have been identified as being predictive of both SR and pharmacological treatment outcomes, many of these studies suffer from small sample sizes and lack of independent replication. Before SR can be confidently identified as a target for pharmacogenetic treatment approaches, additional studies are needed to more clearly characterize how different genotypes relate to specific dimensions of SR as a function of alcohol dosage, limb of intoxication, risk factor under study and stage of alcoholism [28,133].

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