

Application of Human Laboratory Models to Pharmacotherapy Development for Alcohol Dependence

Lara A. Ray^{1,*}, Kent E. Hutchison² and Molly Tartter¹

¹Department of Psychology, University of California Los Angeles, ²Department of Psychology, University of New Mexico, and Mind Research Network

Abstract: Human laboratory studies have a rich history in the alcoholism field and several important determinants of alcohol use disorders have been successfully modeled under controlled laboratory conditions. Laboratory paradigms have been employed to identify biobehavioral risk markers for alcohol misuse and more recently, have been integrated with behavioral genetic, neuroimaging, and pharmacological approaches to further elucidate the neuropathophysiology of addiction and to screen for efficacious treatments. This review will address the rationale and application of human laboratory models to advance pharmacotherapy development for alcohol dependence. It is argued that when properly implemented, laboratory models may help scientists and clinicians understand mechanisms of pharmacotherapy response, which in turn may inform efforts to optimize the currently available and newly developed treatments for alcoholism. Limitations and future directions are discussed.

Keyword: Alcohol, laboratory studies, craving, pharmacotherapy, genetics.

1. INTRODUCTION

Human laboratory studies have a rich history in the alcoholism literature, dating as far back as the post-prohibition era with work by Jellinek and colleagues [1]. Over the years, several important determinants of alcoholism have been successfully modeled under controlled laboratory conditions. These models include alcohol self-administration, [2, 3], cue-reactivity [4-6], alcohol administration in oral [7-9] and intravenous forms [10, 11], stress-induced craving [12-14], subjective responses to alcohol [15], and acute tolerance [16, 17]. A variety of well-validated human laboratory paradigms of alcohol use and misuse are available to researchers in the field. These paradigms have been employed to identify biobehavioral risk markers for alcohol misuse, such as low response to the neuropharmacological effects of alcohol [18, 19]. More recently, these models have been integrated with behavioral genetic, neuroimaging, and pharmacological approaches to further elucidate the neuropathophysiology of addiction and to screen for efficacious treatments. This review will discuss the rationale and application of human laboratory models to pharmacotherapy development for alcohol dependence. We will discuss how these models may help scientists and clinicians understand mechanisms of pharmacotherapy response in order to optimize the currently available and newly developed treatments for alcoholism. Limitations and future directions will be discussed.

2. LABORATORY MODELS OF ALCOHOLISM: AN OVERVIEW

We will first discuss pharmacotherapies for alcoholism that improve drinking outcomes through a variety of neuropharmacological and associated biobehavioral mechanisms. Next we review the biobehavioral mechanisms by which pharmacotherapies for addiction may reach clinical efficacy. This is followed by a presentation of the human laboratory paradigms available to test such mechanisms of action. Biobehavioral mechanisms of action of efficacious pharmacotherapies for alcoholism include the following:

a). *Reduction of Alcohol Craving (Urge to Drink).* Medications may reduce drinking and promote abstinence by dampening

urges to drink and reducing craving for alcohol. Alcohol craving has been examined in many contemporary models of alcoholism [20, 21]. As demonstrated by Monti and colleagues, when exposed to their usual alcoholic beverage, most alcohol dependent individuals respond with increased urge to drink, which is accompanied by psychophysiological reactivity such as increased heart rate, blood pressure, and skin conductance [22, 23]. Importantly, medications that dampen urge to drink hold promise for promoting abstinence and reducing alcohol consumption. Pharmacotherapy studies have shown that naltrexone, a mu-opioid receptor antagonist, reduces urge to drink, as compared to placebo [24, 25]. More recently, gabapentin, an anticonvulsant, was found to reduce alcohol craving and consumption in a laboratory-based model. Gabapentin improved sleep quality in alcohol dependent individuals experiencing protracted abstinence symptoms, thereby suggesting that it ameliorates psychophysiological and cue-induced reactivity during abstinence [26]. However, these promising results are tempered by a null finding indicating that gabapentin did not reduce drinking, dampen alcohol craving, or alter the subjective effects of alcohol in a sample of non-treatment seeking alcohol dependent individuals [27]. More recent findings suggest that gabapentin may be especially useful in reducing alcohol withdrawal symptoms and post-withdrawal drinking [28].

b). *Blunting of the Stimulant Effects of Alcohol.* A medication may reduce alcohol intake by blunting the rewarding and stimulant effects of alcohol. Although not proven to promote abstinence, per se, reward blunting may reduce the likelihood that a "slip" drinking episode results in heavy drinking, and thus prevent relapse. Reward blunting is thought to be vital to naltrexone's effect on drinking outcomes [24, 29]. In brief, pharmacotherapies that can effectively blunt the rewarding and stimulatory effects of alcohol may be useful in decreasing relapse rates and frequency of heavy and harmful drinking episodes. Naltrexone appears to reduce alcohol consumption via reward blunting; for a review and meta-analysis, see [30, 31].

c). *Potentiation of the Sedative and Unpleasant Effects of Alcohol.* A medication may reduce drinking by increasing the likelihood that alcohol intake will lead to sedation, marked by unpleasant and dysphoric feelings such as: feeling down, heavy-headed, sluggish, inactive, and sedated; all items from the Biphasic Alcohol Effects Scale (BAES), Sedation Subscale [32]. Some studies have shown that naltrexone causes an in-

*Address correspondence to this author at the University of California, Los Angeles, Psychology Department, 1285 Franz Hall, Box 951563, Los Angeles, CA 90095-1563; Tel: 301-794-5383; Fax: 310-207-5895; E-mail: lararay@psych.ucla.edu

crease in self-reported fatigue, tension, and confusion [33]. Additionally, naltrexone blunts the tension reduction caused by alcohol during the descending limb of intoxication [34] when the sedative effects of alcohol are most prominent [32, 35]. Disulfiram, the oldest pharmacotherapy approved by the Food and Drug Administration (FDA) for the indication of alcohol dependence, also capitalizes on the unpleasant effects of alcohol. The interaction between disulfiram and ethanol causes sweating, headache, nausea and vomiting, leading the patient to associate the symptoms with alcohol consumption [36]. Poor medication compliance with disulfiram, however, has greatly limited its use in clinical practice [37].

- d). *Increasing Cognitive Control.* Recent pre-clinical work has suggested that effective pharmacotherapies for addiction may increase cognitive control and decrease impulsive decision-making [38, 39]. For instance, a human laboratory study found that acute doses of naltrexone (50 mg) reduced impulsive choice among individuals with an external attribution style [40]. Aripiprazole, a partial dopamine agonist, may also enhance decision-making abilities in response to craving [41]. A human-laboratory study found that aripiprazole disrupted the connection between subjective feelings of craving and alcohol intake, especially for those who ranked low on self-control measures [41]. Finally, Atomoxetine, a non-stimulant medication for ADHD, was found to reduce the urge to drink in response to alcohol challenge for a group of heavy drinkers [42]. Atomoxetine's mechanism of action on alcohol craving may be related to the increase in norepinephrine and pre-frontal cortex dopamine levels which control the "set-point" for alcohol craving [43]. These biological processes may account for the increase in cognitive control, which in turn may help patients establish abstinence.
- e). *Ameliorating protracted withdrawal symptoms.* Protracted withdrawal from alcohol is marked by feelings of anxiety and nervousness, sleep disturbance, and dysphoric mood. These behavioral effects result from chronic alcohol exposure and are thought to be mediated by increased glutamatergic activity and decreased dopaminergic activity in the ventral tegmental area [44]. Medications that can alleviate protracted withdrawal symptoms are thought to promote abstinence and recovery from alcohol use disorders. Acamprosate, a taurine analogue that works as a partial agonist of the NMDA-glutamate receptors and antagonist of the metabotropic glutamate receptors, has been examined as a pharmacotherapy for alcoholism that may alleviate protracted withdrawal symptoms [45, 46]. Pre-clinical and clinical studies have shown that acamprosate alleviates protracted withdrawal symptoms, including sleep disturbances [47, 48]. In a direct comparison of naltrexone and acamprosate, acamprosate was effective in reducing heart rate, a measure of autonomic arousal. Naltrexone performed better than acamprosate in reducing overall craving in dependent alcoholics who had no heavy drinking days for up to 6 weeks [45]. Therefore, although naltrexone appears to be a more effective medication for craving reduction, acamprosate may be especially effective for patients experiencing protracted withdrawal symptoms. As noted above, gabapentin is another promising pharmacotherapy thought to alleviate protracted withdrawal symptoms such as anxiety and negative affect [26, 28].
- f). *Addressing psychiatric comorbidity.* Psychiatric comorbidities are often associated with alcohol use disorders [49, 50] and medications that treat co-morbidity may reduce drinking by targeting emotional symptoms of the comorbid mood disorder that either precipitate or maintain alcoholism. In a recent study, quetiapine, an atypical antipsychotic medication, was found to reduce drinking in patients with Type B alcoholism [51, 52], which is characterized by high severity of depend-

ence, polydrug use and poor prognosis [53]. Patients identified as Type A, which is marked by later onset alcohol dependence and less psychiatric comorbidity, did not benefit from quetiapine to the same extent. These results suggest that quetiapine is differentially effective based on alcohol typology and may be particularly useful in treating alcohol dependent patients with psychiatric comorbidities.

Similarly, the serotonin agonist ondansetron was found to be effective in reducing symptoms of hostility, anxiety and depression among alcohol dependent patients with early age of onset of alcoholism [54]. Early age of onset was associated with more severe alcoholism and greater frequency of depression and anxiety symptoms [54]. However, the same study found that amelioration of mood symptoms did not change drinking behavior. Additional research, including the refinement of alcohol typologies [55] may help clarify the link between mood symptoms and drinking outcomes, which has been muddled by sample heterogeneity.

The selective serotonin reuptake inhibitor (SSRI) sertraline has been studied as a treatment for co-morbid alcohol dependence and major depressive disorder [56, 57]. Although it has been found to reduce drinking [58] and depression symptoms [59], separately, results on the effectiveness of sertraline for co-morbid depression and alcohol dependence have been mixed. Sertraline may, in fact, be most effective for alcohol dependent patients who do not have a history of depression [57]. Fluoxetine, another SSRI, has shown more consistent success in treating mood symptoms and reducing drinking in patients with co-morbid alcohol dependence and major depression [60]. Recent studies have tested fluoxetine as a treatment for adolescents with co-morbid depression and alcohol addiction with generally positive results [61, 62]. However, the findings on fluoxetine's typology-specific effects are mixed [63]. Research on ondansetron, sertraline and fluoxetine suggests that the utility of targeting mood and anxiety symptoms in alcohol dependent patients may vary as a function of alcoholism subtypes [56].

Human laboratory models were developed for the study of alcoholism etiology and have recently been adapted for the study of treatment efficacy mechanisms. These adapted laboratory models focus on different features of the addiction initiation and maintenance process and provide unique targets for intervention. Some of the most widely used human laboratory models of alcoholism are described briefly below:

a) *Subjective Responses to Alcohol.* Individuals vary widely in their subjective experience of the pharmacological and neurobehavioral effects of alcohol upon consumption [64, 65]. While some individuals may be more or less sensitive to the positively reinforcing and stimulant effects of alcohol, others report higher sensitivity to the aversive, sedative effects. Alcohol administration studies have documented substantial variability in subjective responses to alcohol and have shown that differences in these subjective experiences may play a significant role in the predisposition to alcohol use and misuse [19]. Research suggests that the way in which individuals experience the pharmacological effects of alcohol influences their subsequent use of alcohol [66, 67] and the risk of developing an alcohol use disorder [19]. Moreover, subjective responses to alcohol are heritable [68, 69] and informative regarding the neuropharmacological effects of alcohol and their biological and genetic bases, thereby representing important biobehavioral phenotypes for alcoholism vulnerability [65, 70]. Subjective responses to alcohol represent an important target for alcoholism pharmacotherapy and medications that reduce the reinforcing effects of alcohol, such as naltrexone [33, 71, 72], may be ultimately effective in reducing alcohol use. For example, a recent study by Miranda *et al.* found that topiramate may be effective in reducing alcohol intake by altering subjective response to alcohol, despite not evidence of topiramate-induced changes in alcohol craving [73].

A variety of methods have been used to examine the subjective effects of alcohol. While often congruent, these approaches can differ by method of administration, dose of alcohol, and the measures used to capture the effects of alcohol. Most studies have administered alcohol orally, which results in enormous variance in blood alcohol levels, even after the dose is adjusted for gender and weight [25]. This variation in blood alcohol level significantly limits interpretation of the findings and has led to the use of intravenous administration of 5% ethanol. Subjects can then be "clamped" at a precise blood alcohol level for more accuracy [74]. Studies also vary by the amount of alcohol used, with blood alcohol levels generally in the range of .02 to .10. Given that the subjective effects of alcohol differ substantially as a function of dose, it is critical to account for dose when interpreting the results of studies.

Most recently, a method called computer assisted self-infusion of ethanol (CASE) was developed to allow participants to increase their blood alcohol level precisely with the push of a button, that in turn controls an IV pump and delivers controlled doses of alcohol [75, 76]. This promising new technology allows researchers to examine the relative reinforcing value of alcohol thru behavioral samples and to employ a self-administration paradigm that nicely parallel the progressive ratio schedules seen in pre-clinical models. A practice session is needed before good test-retest reliability is reached [76]; nevertheless this novel method is promising as it affords experimenters with several parameters to manipulate, which in turn may reveal unique laboratory-based alcohol use phenotypes.

Finally, a variety of measures are used to quantify the effects of alcohol. A number of studies have focused on measures of stimulation and sedation using the Biphasic Alcohol Effects Scale (BAES) as well as mood (e.g., the Profile of Mood States). Other studies have focused on subjective intoxication and objective measures such as body sway [77]. More recently, studies have incorporated behavioral measures, such as the quantity of drinking in the context of alternative rewards, usually varying monetary amounts [78]. In sum, there are a number of methodological differences across laboratory studies that must be considered when using these models to screen or test medications for alcoholism.

b) Alcohol Craving. Alcohol craving has been defined as a strong desire to consume alcohol in the presence of alcohol cues (i.e., cue-induced craving or reminders of alcohol use) or small alcohol priming doses (i.e., alcohol-induced craving). There is considerable evidence that small priming doses of alcohol increase the desire for alcohol [8] and the likelihood that the individual will consume alcohol [79]. Craving for alcohol has, in turn, been associated with loss of control over drinking, which is part of the alcohol dependence criteria, as defined in DSM-IV. Alcohol-induced craving has been the target of treatments for alcoholism [80-82], and has been studied using laboratory conditions shown to reliably induce craving responses [4, 83, 84]. From a biological standpoint, alcohol craving has been associated with dopaminergic brain activity, primarily in the mesolimbic area [8]. Alcohol craving represents an important determinant of drinking, particularly among alcohol dependent individuals and those in recovery.

However, behavioral measures of subjective craving or measures of autonomic symptoms of craving like increased heart rate and skin conductance do not always predict drinking outcomes. For example, although acamprosate reduces heart rate and skin conductance more effectively than naltrexone, naltrexone is more effective at reducing alcohol intake [45, 85]. Additionally, subjective craving has been inconsistently linked with drinking outcomes when measured using categorical ratings or visual analogue scales [86-88]. Understanding the factors that lead to craving is critical, as a reduction in craving is often the target of behavioral and pharmacological interventions [89, 90]. However, there has been some controversy about the role and definition of craving and the way it is conceptualized in animal and human models [91].

Recent advances in imaging technology have provided the field with a paradigm to define phenotypes that can be used to identify pharmacotherapies that effectively reduce craving for alcohol. For example, blood oxygen level dependent (BOLD) measures of activation of the ventral tegmental area (VTA), nucleus accumbens (NAC), and prefrontal areas have been used to identify the putative biological mechanisms of craving. Recent reviews of the addiction neuroimaging literature suggest that the orbitofrontal cortex (OFC), anterior cingulate, amygdala, thalamus, striatum, VTA and the connections among these structures underlie the development and experience of craving, loss of control over substance use, and relapse across several substances including alcohol, cocaine, heroin, methamphetamine, and tobacco [92-94]. Recent work has also suggested that mesocorticolimbic activation in response to alcohol cues is associated with severity of dependence [95, 96]. Thus, neuroimaging technology, such as BOLD response and fMRI, offer a more direct assessment of the neurobiological mechanisms that underlie subjective craving, as opposed to alternative laboratory methods that measure subjective craving via questionnaire or autonomic arousal.

c) Stress Models of Drinking. The maintenance of alcoholism is believed to occur through neuroadaptation in stress-pathways and interactions with the reward and motivational circuitry of the brain [97, 98]. Laboratory models of stress and stress-induced craving have focused on exposure to stressors under controlled conditions including imaginal exposure [12, 14], physical stressors, such as the cold pressor task [99, 100], and social stressors, such as public speaking and arithmetic problem-solving using the Trier Social Stress Test [101]. These paradigms have found strong stress-induced urge to drink among alcohol dependent individuals [12], but a less robust relationship between stress and alcohol craving [12] and ad-lib alcohol use among social drinkers [101]. From the evidence, it seems that stress-induced drinking may develop with an alcohol problem, and is not a marker of susceptibility or risk. This explanation of stress-induced drinking is consistent with the neurobiological theory that neuroadaptation in stress pathways occurs during the development of addiction [102, 103].

As with subjective responses to alcohol and alcohol craving, stress-induced craving and drinking represent another important therapeutic target for alcoholism. Several studies have shown an association between physiological and psychosocial measures of stress and subsequent relapse among alcohol dependent individuals in treatment [104]. Medications that can attenuate the connection between stress and craving or drinking outcomes may be clinically useful in preventing relapse. A recent study found that lofexidine may ameliorate stress-induced drug craving as assessed in the laboratory [105]. Although stress models have not been used to study alcoholism pharmacotherapies to the same extent as subjective response and craving models have, they offer a unique phenotype that is of high clinical and empirical significance to the phenomenology of alcoholism.

3. LABORATORY STUDIES AND THE DEVELOPMENT OF ALCOHOLISM ENDOPHENOTYPES

Recent research and theory in psychiatric genetics has increasingly recognized the heterogeneity of diagnostic phenotypes. These developments argue for more narrowly defined and homogeneous behavioral phenotypes, or intermediate (endo)phenotypes for psychiatric disorders [106, 107], including addictions [70, 108]. Laboratory studies offer a unique opportunity to refine alcoholism phenotypes and to generate useful endophenotypes for pharmacology development. A more discrete phenotype is thought to increase statistical power to detect significant associations and facilitates the interpretation of the findings. Ideally, a behavioral phenotype is narrowly defined, readily identifiable, empirically related to the clinical manifestation of the disorder, related to an underlying biological mechanism, and theoretically related to a candidate gene.

The intermediate phenotype approach has already allowed for progress in genetic association studies. Significantly, this approach not only increases power to detect genetic effects, it also allows us to ask different research questions about the neurobiology and mechanisms underlying disease processes and pharmacotherapy response [108]. Examples of laboratory-based intermediate phenotypes for alcoholism include craving for alcohol, alcohol-induced reward, reinforcing value of alcohol, and response inhibition processes. These phenotypes can be leveraged as discrete and mechanistic targets to examine genetic determinants of medication response. When applied to pharmacotherapy research, intermediate phenotypes allow us to examine mechanisms of medication response that go beyond drinking outcomes. These phenotypes can be leveraged to examine genetic determinants of medication response on those discrete and mechanistic targets. These efforts have tremendous potential to advance pharmacogenetic efforts in addiction, as discussed in detail below.

In response to the literature on intermediate phenotypes for psychiatric disorders and their potential to advance etiological and treatment approaches to these disorders, we have recently proposed our own conceptual model that integrates intermediate phenotypes of alcoholism with genetic factors and pharmacological treatments for addictions [65]. In this model, we posit that alcohol intermediate phenotypes and genetic factors can be used to improve our understanding of pharmacotherapies for alcoholism in several ways (see Fig. 1). First, intermediate phenotypes such as craving and subjective responses to alcohol have been shown to predict drinking behavior and the risk for developing alcohol use disorders [19, 109–111]. Second, medications found to operate at the level of intermediate phenotypes, such as craving and subjective responses to alcohol [83, 112, 113], may be ultimately effective in reducing drinking. Third, genetic variants may underlie the expression of alcohol intermediate phenotypes such as subjective responses to alcohol [10, 113]. Fourth, genetic variants underlying alcohol intermediate phenotypes may be used to predict responses to pharmacotherapies thought to affect those phenotypes [113]. This model is interdisciplinary by nature, as it integrates aspects of behavioral genetics, pharmacology, clinical and experimental psychology. By focusing on theory-driven alcohol intermediate phenotypes and the genetic factors underlying these phenotypes, progress can be made toward elucidating pharmacotherapy mechanisms and genetic moderators of medication response. In brief, the proposed model seeks to facilitate research that integrates pharmacotherapies for alcoholism, ge-

netic predictors of medication response, and drinking outcomes by providing laboratory-based intermediate phenotypes that are mechanistic in nature and may serve as treatment targets.

4. LABORATORY STUDIES AND PHARMACOTHERAPY FOR ALCOHOLISM: RATIONALE

There is increasing recognition of the importance of identifying the mechanisms of action of pharmacotherapies for alcoholism. While clinical trials are essential for testing pharmacotherapies at the level of alcohol use outcomes, laboratory studies have provided a more nuanced test of the mechanisms of drug action both at the biological and the behavioral levels. Novel approaches to studying these pharmacotherapies in the laboratory have shed light on their efficacy using a more internally valid approach. Several recent pharmacology studies have addressed biobehavioral risk markers as the cause of variation in medication response. These markers can improve treatment outcomes by allowing clinicians to match patients to medications using drinking profiles and biobehavioral risk markers. In brief, increased knowledge of these risk markers can lead to targeted treatments, more individualized treatment regimens, and ultimately, better clinical outcomes for patients suffering from alcohol use disorders.

5. LABORATORY STUDIES AND PHARMACOTHERAPY FOR ALCOHOLISM: APPLICATIONS

Laboratory paradigms for alcoholism have been used to test the initial efficacy of medications for alcoholism, while also examining possible causes of heterogeneity in treatment outcome. Some examples of the application of laboratory phenotypes to pharmacotherapy development for alcoholism are discussed below. A summary of laboratory-based approaches to studying alcoholism pharmacotherapies is provided in Table 1.

A. *Aripiprazole and inhibitory-control.* Variation in response to aripiprazole for alcoholism may be moderated by intermediate phenotypes of the dopaminergic system *via* GABA and glutamate processes. While dopamine is often implicated in the rewarding and positive reinforcement effects of alcohol and other drugs, it is also critical to inhibitory control or, colloquially, the ability to inhibit impulsive responses, such as drinking while trying to abstain [41, 114]. In contrast to other pharmacotherapies for alcoholism that act on the dopamine system, aripiprazole appears to act as a dopamine stabilizer [115].

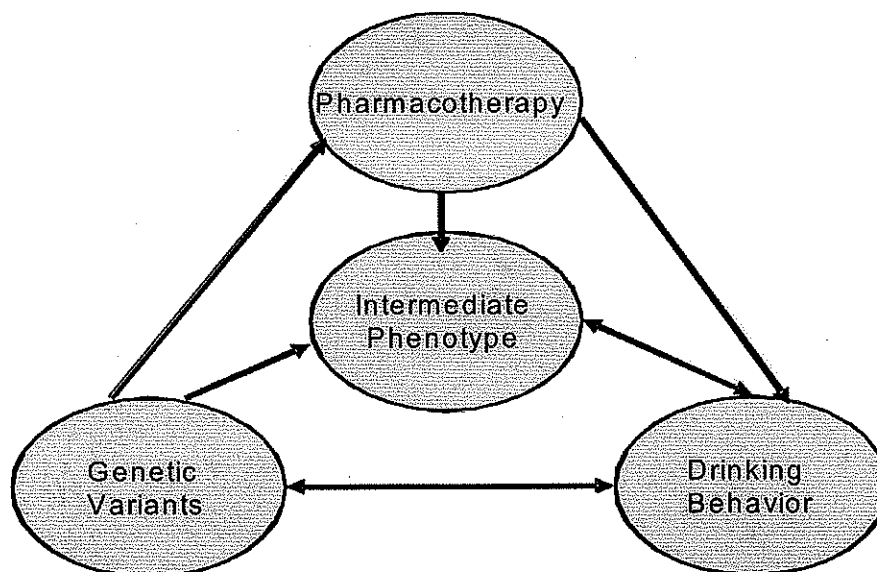


Fig. (1). Conceptual model of laboratory-based alcoholism endophenotypes and how these can be used to triangulate between pharmacotherapy effects, genetic predictors of response, and ultimately, drinking outcomes.

Table 1. Examples of Laboratory Paradigms Applied to Pharmacotherapy Development for Alcoholism

Laboratory Paradigm	Phenotype/Mechanism of Action	Pharmacotherapy	Outcome	Citations
Positive and negative affective drinking cues	Cue-induced craving	Gabapentin	Decreased positive affect-induced craving	[26]
Delayed discounting task	Inhibitory control	Naltrexone	Reduced impulsive responding	[40]
Alcohol self-administration in a naturalistic setting	Priming dose craving	Naltrexone	Decreased self-administration, slower drinking progression	[78]
Alcohol administration	Subjective responses to alcohol	Naltrexone	Decreased stimulation	[24, 25, 29, 33]
Stress Induction	Stress-induced craving	Lofexedine	Increased sedation	[105]
Initial priming and self-administration of alcohol	Low self-control	Aripiprazole	Break in alcohol-induced stimulation leading to increased consumption	[41]
Alcohol cue-exposure	Negative affective withdrawal symptoms	Acamprosate	Reduction of autonomic nervous system reactivity, no decrease in craving	[130]
Priming dose of alcohol and cue-exposure	Cue and priming dose-induced craving	Olanzapine	Reduction in craving, mediated by DRD4 polymorphisms	[83, 143]

In a laboratory study of inhibitory control and drinking outcomes, aripiprazole (15 mg/day) was found to help non treatment-seeking alcoholics reduce their drinking in both a natural setting and in the laboratory using a monetary choice paradigm [41]. Interestingly, aripiprazole reduced drinking most dramatically for participants with low self-control or high impulsivity during the naturalistic drinking period. This improved decision-making may be the result of more balanced dopaminergic functioning. Moreover, a negative association was found between self-reported stimulation after the first drink and the number of drinks subsequently consumed in the aripiprazole-treatment group. Together, these results suggest that although alcohol craving was not altered by aripiprazole treatment, the connection between alcohol reinforcement and alcohol intake was disrupted, possibly *via* improved inhibitory control. Koob and Le Moal (2001) have convincingly argued that heavy drinking leads to a hypodopaminergic state, which in turn leads to craving. A disruption in dopamine functioning may be central to the development of cue-induced craving and inhibitory control deficits that underlie addiction [114]. Thus, it is plausible that restored inhibitory control with aripiprazole may be attributed to dopamine changes. Aripiprazole's effect on inhibitory control in response to alcohol craving also illustrates how an ideal laboratory paradigm adds knowledge not only of medication effectiveness but of the heterogeneity of alcohol disorders and the mechanism of treatment response.

B. *Gabapentin, cue-induced craving, and positive affect.* Gabapentin is an anticonvulsant that has been successful in treating symptoms of depression [116], insomnia in alcohol withdrawal [117] and anxiety symptoms during alcohol withdrawal [118]. Gabapentin acts on the GABA and glutamate systems to reduce central nervous system activity. It follows that gabapentin may help ameliorate anxiety and other negative affective symptoms associated with protracted withdrawal during early recovery from alcoholism. Gabapentin was recently found to attenuate craving among cue-reactive, alcohol dependent subjects [26]. Interestingly, gabapentin helped reduce alcohol craving evoked by positive affect-associated cues, but did not help reduce craving due to negative affect-associated cues. Reduction of negative affect has been hypothesized as a mechanism for maintaining abstinence from alcohol because

of the consistent association between negative affect and relapse [13]. The contrast between the findings that gabapentin ameliorates anxiety and depression but is ineffective in reducing negative mood in a cue-reactivity paradigm suggest that further study is needed to fully understand gabapentin's mechanism of action on craving. Importantly, this study illustrates how laboratory paradigms can highlight inconsistent findings on the mechanisms of pharmacotherapy efficacy and indicate a direction for further study.

C. *Naltrexone and alcohol self-administration.* The release of dopamine is a biological process that underlies the reinforcing effects of alcohol [119] and naltrexone may reduce drinking *via* suppression of the dopaminergic system. It is generally posited that naltrexone works by occupying opioid receptors preventing the binding of such receptors by endogenous opioid peptides released upon alcohol intake, which in turn prevents the γ -aminobutyric acid (GABA)-mediated release of dopamine in the ventral tegmental area thereby putatively blocking alcohol's reinforcing effects [120, 121]. Opioid peptides may also play a role in alcohol and drug reward through dopamine independent pathways [122]. Alcohol self-administration is a unique alcohol laboratory paradigm designed to replicate alcohol use in the natural environment. Naltrexone was tested using a self-administration task combined with a monetary incentive to abstain from drinking as a further check for environmental validity of the outcomes [78]. In the self-administration paradigm, participants treated with naltrexone consumed fewer drinks over two hours than placebo-treated individuals, with the greatest difference in the second hour. This pattern suggests that alcohol interacts with naltrexone to curb craving over drinking time. Naltrexone also reduced alcohol craving when compared to placebo even before the priming dose of alcohol was consumed, suggesting that alcohol is not essential to naltrexone's ability to reduce craving. Latency between drinks has been conceptualized as a measure of craving [123], and naltrexone-treated participants consumed their drinks more slowly, suggesting that the effects of naltrexone on craving may in part be alcohol-mediated.

- D. *Acamprosate, negative affect and relief craving.* Acamprosate is thought to aid in reducing the negative affect and anxiety symptoms of alcohol withdrawal [124], also called "relief craving", thought to characterize a subset of patients trying to establish abstinence. Acamprosate has been found to reduce glutamate activity in rats [125], and it is postulated that a hyper-glutamatergic state in humans produces the "relief craving" associated with acute and protracted ethanol withdrawal. Acamprosate may reduce these feelings by returning glutamate activity to homeostasis [126, 127]. Acamprosate has been found to reduce craving in an alcohol-dependent population after a priming dose of alcohol [128, 129]. Acamprosate has also been compared to naltrexone using an affective cue-exposure in dependent but abstinent patients to induce craving for alcohol in a study of relief craving [130]. Cue-induced subjective craving was measured as well as activation of the autonomic nervous system using heart-rate and skin conductance. Although naltrexone reduced overall craving significantly more than acamprosate, acamprosate was found to reduce heart rate compared to naltrexone and placebo, at the trend level. This provides partial support for the hypothesis that acamprosate is effective for patients experiencing autonomic arousal symptoms that lead to relief craving: part of the phenomenology of protracted withdrawal that ensues upon establishment of abstinence after chronic alcohol exposure. In addition to the demonstration of the utility of the laboratory paradigms to parse mechanisms of medication effects, this study nicely demonstrates the opportunity to compare pharmacotherapies for alcoholism using laboratory-based methods.

6. PHARMACOGENETICS OF ALCOHOLISM TREATMENT

Inheritance patterns were first utilized in choosing pharmacotherapy in the 1950s, when variance in medication response was used to construct studies of drug response and metabolism phenotypes at the population level, and from there, biochemical and genetic bases of gene by pharmacotherapy interaction were unraveled [131]. Rapid genetic sequencing now allows us to test genetic predictors of treatment outcomes based on known biochemical pathways and drug mechanisms [131, 132]. Genetic variation in neurotransmitter systems leads to brain-based and behavioral phenotypes of varying susceptibility to alcohol dependence. Even within the phenotypes that confer the greatest susceptibility to addiction, variation exists in the mechanisms of addiction and pathways by which one becomes alcohol dependent. As discussed in detail above, human laboratory studies provide useful information on the mechanisms of action of pharmacotherapies for addiction. These medications can be targeted by identifying which agents work best for a behavioral risk marker, as discussed with naltrexone, aripiprazole, acamprosate and gabapentin.

Studies that incorporate genetics into the study of medication response can explain even more of the variance in pharmacotherapy outcomes. While genetic studies have examined susceptibility to alcoholism as a whole [133, 134], pharmacogenetic studies can isolate polymorphisms that account for pharmacotherapy effectiveness for alcoholism [135]. Examining polymorphisms suspected to alter a pharmacotherapy's tolerance levels, toxicity and effectiveness may lead to more effective and safer pharmacological treatments. Although pharmacogenetic studies applied to alcoholism are incipient, some important findings have already emerged.

One of the most notable pharmacogenetic findings in alcoholism is the association between a polymorphism of the mu-opioid receptor (OPRM1) gene and the response to naltrexone. Naltrexone's effect results from occupying mu-opioid receptors in the brain's reward pathway [136]. When unoccupied, mu-opioid receptors bind beta-endorphins triggering a G-protein signaling pathway that changes neuronal activation and ultimately reduces dopaminergic

activity in the striatum. The association between naltrexone response and genetic variation in the OPRM1 gene represents an interesting pharmacogenetic effect, given that this non-synonymous mutation (Asn40Asp) in the gene coding for mu-opioid receptors, the primary target of naltrexone, has reported functional significance. Specifically, the Asp40 allele has been associated with greater affinity of mu-opioid receptors for beta-endorphins and a greater response to both alcohol and opioid antagonists [10, 137]. Together, these findings on the functional polymorphism in the gene coding for the primary pharmacodynamic target of naltrexone make the affinity of mu-opioid receptors for beta-endorphins a theoretically plausible pharmacogenetic effect.

Oslin and colleagues (2003) were the first to test this effect in a reanalysis of two clinical trials of naltrexone and their results suggested that carriers of the minor (asp40) allele had a better clinical response to naltrexone, demonstrated by lower relapse rates and longer time to return to heavy drinking. More recently, the COMBINE Study [135] examined the effect of mu-opioid receptor functional polymorphisms on naltrexone response and found that patients with at least one copy of the Asp40 allele were 5 times more likely to have a good clinical outcome with naltrexone than homozygotes for the Asn40 allele. No genotype effects were found in the control condition, indicating that naltrexone treatment may be optimized when used in concert with genotyping. Recent clinical studies have found further support for this pharmacogenetic effect [132, 138], while others have reported null findings [139].

Importantly, laboratory studies of naltrexone pharmacogenetics have contributed to our understanding of the mechanisms of action underlying differential clinical response to naltrexone. Ray and Hutchison (2007) have found that naltrexone produced greater blunting of alcohol reward and alcohol "high" among carriers of the Asp40 allele, providing a mechanistic link between this polymorphism and improved clinical response to naltrexone for alcoholism [113]. A previous human laboratory administration study found that carriers of the Asp40 allele were more responsive to the subjective and reinforcing effects of alcohol [10], and additional studies have implicated OPRM1 polymorphism in greater BOLD response to alcohol cues [140] and greater automatic response to appetitive (non-alcoholic) stimuli [141]. In sum, these results suggest that naltrexone's effectiveness can be maximized by tailoring its use to OPRM1 polymorphism. Equally valuable is the general finding that OPRM1 polymorphism does not predict alcohol dependence [142], highlighting the need to study genes that influence treatment outcome separately from genes that influence onset and maintenance of alcohol use disorders.

Another application of human laboratory designs to alcoholism pharmacotherapy development and pharmacogenetics is that of olanzapine and the dopamine D4 receptor gene (DRD4). Hutchison *et al.* built on their own work on the DRD4 dopamine receptor variable number of tandem repeats (VNTR) polymorphism and alcohol craving [109, 143] to determine whether this polymorphism predicts treatment outcomes with olanzapine, a dopamine antagonist that acts on D2 and D4 receptors in the dopaminergic system [84]. In a previous study, Hutchison showed that the DRD4 polymorphism accounted for variability in craving after a priming dose of alcohol [109]. Hutchison also found that olanzapine was effective at reducing craving induced by a priming dose of alcohol and alcohol cues [84]. It follows from these two findings that the DRD4 VNTR may lead to variability in olanzapine treatment outcomes. In a combination of a clinical trial with a laboratory-based cue-reactivity paradigm, Hutchison and colleagues (2006) found that olanzapine reduced alcohol craving among Long (≥ 7 repeats) allele carriers of the DRD4 VNTR but not among homozygotes for the Short (< 7 repeats) allele, suggesting that this polymorphism predicts both higher craving and better olanzapine response.

In summary, there is a great deal of interest in personalized treatment approaches for medical conditions, including psychiatric

disorders such as addiction. The findings of naltrexone pharmacogenetics for alcohol dependence hold promise for developing more targeted therapies for these complex disorders [144]. Importantly, the pharmacogenetic studies reviewed above demonstrate the use of laboratory-based alcohol phenotypes in parsing out the mechanisms of risk and response efficacy for alcoholism pharmacotherapies.

7. LIMITATIONS & FUTURE DIRECTIONS

Despite great progress over the years, human laboratory approaches to alcoholism have immense opportunity for further development. Establishing the predictive utility of laboratory-based phenotypes using longitudinal research approaches is essential to the progressive integration of laboratory models with treatment development for alcohol use disorders. Such studies are needed to ascertain the predictive power of laboratory phenotypes both as markers of the risk for the disorder and, in the case of pharmacotherapy development, as valuable indicators of medication response in clinical settings. Laboratory studies conducted in the context of clinical trials may be particularly useful in examining mechanisms of medication response while also connecting laboratory-based assessments to treatment outcomes.

As discussed in this review, laboratory studies of alcoholism have been leveraged to refine alcohol phenotypes and inform behavioral genetics research. However, several opportunities remain in both areas. Alcohol phenotypes can be further refined through innovative laboratory manipulations and combinations of established paradigms (e.g., stress induction followed by alcohol administration). Laboratory phenotypes can parallel with important neurobiological constructs in addiction theory have enhanced translational value and can draw upon these theories to elucidate underlying pathophysiology of the disorder.

Moreover, in order to best understand the genetic implications of these laboratory phenotypes, attention must be paid to recent developments in psychiatric genetics in order to determine the optimal contribution of laboratory-based studies. The development of rapid genotyping technologies that allow for Genome Wide Association Studies (GWAS) continue to have a huge impact on the field of alcohol addiction research. Although the ability to probe the whole genome for associations is exciting, the sample size requirements for adequately powered studies has increased dramatically and estimates suggest a minimum required sample of 1,000 participants. These requirements are largely not feasible from a laboratory studies perspective, as laboratory studies are more time intensive than self-report assessments. Nevertheless, laboratory phenotypes are useful in genetics research. For example, laboratory studies can be used to probe for promising results from large scale genetic analysis, providing a more focused and theory-driven level of analysis. Additionally, laboratory studies may be used to validate self-report measures that can in turn be used for efficient large scale data collection.

Yet another important avenue for further research in human laboratory approaches to alcoholism is the combination of laboratory and neuroimaging paradigms. These efforts may be useful for elucidating the neural basis of constructs such as alcohol craving, subjective responses to alcohol, and stress-induced craving. In turn, knowledge of the neural basis of addiction can inform the treatment of novel development approaches. Experimental phenotypes and neuroimaging techniques can also be combined to study pharmacology. This approach allows us to answer empirical questions about the pharmacological intervention, the behavioral phenotype, and the neural activation produced by both the pharmacological and the behavioral paradigms. In brief, the integration of laboratory paradigms, pharmacology, and neuroimaging methods is particularly promising as it allows for the ascertainment of both behavioral and brain-based probes of pharmacotherapy effects.

In conclusion, laboratory studies of alcoholism have a rich history marked by multiple contributions to the understanding of alco-

holism etiology and treatment. Some questions remain about the predictive utility of these phenotypes and careful examination through longitudinal designs is required. The success of the next generation of laboratory studies of alcoholism hinges upon the ability to effectively integrate these experimental phenotypes with novel technologies and research questions, particularly those pertaining to alcoholism neurobiology. As highlighted by Heilig and colleagues in a recent review of pharmacotherapies for alcoholism, translating neuroscience insights into clinical treatments will be critical to medication development efforts [145]. To that end, laboratory studies that can effectively link to pre-clinical and clinical efforts may be especially useful in the context of translational approaches to alcoholism treatment development.

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