# Naltrexone for the Treatment of Alcoholism: Clinical Findings, Mechanisms of Action, and Pharmacogenetics

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**Abstract:** Naltrexone is an opioid receptor antagonist with established efficacy, albeit moderate, for the treatment of alcohol dependence. This manuscript provides a critical review of the literature on naltrexone as a pharmacotherapy for alcoholism by covering the following areas: (a) clinical findings from treatment studies; (b) pharmacokinetics and safety data; (c) medication compliance and persistence; and (d) neurobiological and biobehavioral mechanisms of action of naltrexone for the indication of alcohol dependence. This review will then focus on the emerging literature on naltrexone pharmacogenetics, which has the potential to identify responders on the basis of genetic variation and to use genetic tools to individualize the use of this medication. Limitations and future directions in the research and practice of naltrexone for alcoholism are also outlined.

**Keywords:** Naltrexone, alcoholism, mechanisms, neurobiology, pharmacogenetics.

## INTRODUCTION

Alcohol abuse and dependence represent two frequently occurring psychiatric conditions. Recent findings from the largest epidemiological study of alcohol use disorders, the National Epidemiological Survey on Alcohol and Related Conditions [1], found that the 12-month prevalence of alcohol dependence in the adult population in the U.S. was 3.8%, while the prevalence of alcohol abuse was 4.7% [2]. These results indicate that 8.5% of the adult population in the U.S. suffers from an alcohol use disorder in a one-year period, which translates into 17.6 million adults affected by alcohol abuse or dependence [2]. Alcoholism represents a significant public health concern associated with an estimated annual cost of $185 billion [3]. Alcohol use disorders are major contributing factors to injuries, medical, and psychiatric illnesses and alcoholism is estimated to cause more than 100,000 deaths annually [4]. According to the U.S. Centers for Disease Control and Prevention, excessive alcohol consumption is the third leading cause of preventable death in the United States [5]. Likewise, the World Health Organization ranks alcohol third among preventable risk factors for premature death in developed nations [6]. Although treatments for alcoholism have improved in recent decades [7], there is still great need to develop more effective interventions for alcoholism. There is also the need to optimize available treatments by identifying responders and individualizing treatment approaches.

This review of the literature on naltrexone will cover various lines of research on naltrexone for the treatment of alcohol use disorders. Specifically, we will address the following areas of inquiry: (a) clinical findings from treatment studies; (b) pharmacokinetics and safety data; (c) medication compliance and persistence; and (d) neurobiological and biobehavioral mechanisms of action of the use of naltrexone for alcoholism. We will also review the emerging research on naltrexone pharmacogenetics, which has the potential to identify responders on the basis of genetic variation and to use genetic tools to individualize the use of this medication. Lastly, we discuss limitations and future directions in the research and practice of naltrexone for alcoholism.

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## CLINICAL FINDINGS

Pharmacotherapies for alcoholism are used less often than psychosocial interventions [8]. The limited use of pharmacotherapy for alcoholism is due, in part, to the relative lack of pharmacological options to treat alcohol use disorders. Specifically, the only pharmacotherapies currently approved by the U.S. Food and Drug Administration (FDA) for the treatment of alcohol dependence in the United States are disulfiran (Antabuse®), naltrexone (Revia®), acamprosate (Campral®), and Vivitrol, an injectable extended-release formulation of naltrexone [9, 10].

Shortly after two initial trials suggested that naltrexone resulted in significantly fewer drinking days and lower rates of relapse after three months of treatment [11, 12], naltrexone was advanced as one of the more promising pharmacological interventions for alcohol dependence [13]. These initial results have been largely supported by more recent trials of naltrexone that generally demonstrate beneficial effects in terms of reducing heavy drinking rates, particularly among those who are compliant with the medication [14-17]. Studies have found that naltrexone reduces the occurrence of heavy drinking days [18-20], increases time to first relapse [16, 21, 22], yields lower relapse rates [12, 23, 24], reduces the number of drinking days [11, 12], reduces the number of drinks per drinking episode [11, 14, 15, 22], and extends the latency to first and second drink among social drinkers [25]. Support for naltrexone, however, is not uniform. A few trials, including a large multi-site trial, have reported no significant outcome differences between naltrexone and placebo-treated patients [26, 27]. However, a recent trajectory-based re-analyses of two negative clinical trials of naltrexone suggested that naltrexone may have a clinically meaningful effect in decreasing the risk of heavy drinking and increasing the likelihood of abstinence from alcohol in those initially null-effect trials [28].

## DOSE RESPONSE FINDINGS

Only three studies to date have examined the dose-dependent effects of naltrexone [29-31] and suggest positive dose-dependent effects. Results suggested a benefit of 100 mg/day over 50 mg/day in decreasing "liking of the alcohol" [29] and reducing drinking in the experimental research laboratory setting, but only among family history positive individuals [30]. Specifically, in the study by Krishnan-Sarin and colleagues [30], non-treatment seeking alcohol-dependent patients consumed significantly less alcohol in the laboratory following a priming dose after taking 100 mg of

1871-5273/10 $55.00+.00 

naltrexone per day for six days. These findings were, however, specific to individuals with a family history positive for alcoholism. The study by McCaul and colleagues [29] examined subjective response to alcohol relative to 0, 50, and 100 mg/day of naltrexone and found that 100 mg of naltrexone was associated with "best effects" marked by decreased liking of alcohol upon exposure. Secondary analyses of McCaul *et al*. [29], in which serum samples from heavy drinkers (described above) were compared for levels of 6-β-naltrexol, the major metabolite of naltrexone, indicated that higher doses of naltrexone resulted in increases in 6-β-naltrexol levels and importantly, that higher levels of 6-β-naltrexol were in turn associated with higher ratings of sedation before alcohol consumption and lower ratings of alcohol liking and best effects upon consumption.

However, the most recent study to date suggests best effects for lower doses. In a smoking cessation trial enrolling non-treatment seeking hazardous drinkers to four naltrexone conditions (placebo, 25 mg, 50 mg, 100 mg), O'Malley *et al*. [31] reported that subjects in all active medication groups were significantly more likely to discontinue meeting hazardous drinking criteria compared to placebo and only the 25 mg dose demonstrated a significantly shorter time to remission of hazardous drinking than placebo. Throughout the course of the study, dose adjustments were made for subjects taking 50 mg (8%) and 100 mg (10.7%) while none were made for those in the 25 mg or placebo condition, although the percentage of reported adverse events was not significantly different between groups. This indicates that the 25 mg dose may be most favorable in consideration of both drug efficacy and a reduction of side effects requiring dose adjustment. However, this sample was ascertained for smoking and the implications of these findings are limited to combination therapies for smoking cessation.

A dose-dependent effect was also observed for the injectable formulation of naltrexone [32, 33]. The efficacy of extended-release naltrexone 380 mg versus 190 mg was compared in a subgroup that had been abstinent for 4 days prior to treatment during an alcohol-dependent placebo-controlled trial. Subjects in the 380 mg condition were found to have a significantly higher rate of initial abstinence, longer time to first heavy drinking episode, fewer heavy drinking days and decreased gamma-glutamyl transpeptidase levels compared to placebo, while data for the 190 mg group showed intermediate, nonsignificant differences compared with placebo [32]. Ciraulo and colleagues [33] also found that extended-release naltrexone 380 mg significantly reduced the number of participants reporting heavy drinking and daily drinks consumed in alcohol dependents; these effects took place within two days of the injection and persisted throughout the 24-week study. Higher dose injectable naltrexone appears to be effective and may encourage adherence and continuation of treatment by producing an early treatment response.

These findings suggest that the effects of naltrexone on subjective responses to alcohol may be dose-dependent and that naltrexone may be targeted on the basis of individual differences. Moreover, these results should be interpreted in the context of the neurobiological effects of naltrexone reviewed above. Specifically, positron emission tomography (PET) studies have found that at a dose of 50 mg/day, naltrexone produces nearly complete blockade of μ-opioid receptors [34-36], compared to an estimated 21% blockage of δ-opioid receptors [36], and presumably lower occupancy of κ-opioid receptors, suggesting that attention should also be paid to κ and δ receptors when examining the dose-dependent effects of naltrexone, particularly as a source of individual differences in clinical response.

## PHARMACOKINETICS AND SAFETY

Naltrexone and its major active metabolite 6-β-naltrexol are competitive antagonists at μ- and κ-opioid receptors, and to a lesser extent at δ-opioid receptors. Although well-absorbed orally, naltrexone is subject to significant first pass metabolism with oral bioavailability estimates ranging from 5 to 40%. The activity of naltrexone is believed to be due to both parent and the 6-β-naltrexol metabolite. Both parent drug and metabolites are excreted primarily by the kidney (53% to 79% of the dose); however, urinary excretion of unchanged naltrexone accounts for less than 2% of the elimination pathway. The plasma half-lives of naltrexone and the 6-β-naltrexol metabolite are approximately 4 hours and 13 hours, respectively. Two other minor metabolites are 2-hydroxy-3-methoxy-6-(β)-naltrexol and 2-hydroxy-3-methyl-naltrexone. Naltrexone and its metabolites are also conjugated to form additional metabolic products. Following oral administration, naltrexone undergoes rapid and nearly complete absorption with approximately 96% of the dose absorbed from the gastrointestinal tract. Peak plasma levels of both naltrexone and 6-β-naltrexol occur within one hour of dosing. Given the known pharmacokinetics of oral naltrexone, a single daily dose of 50 mg is thought to produce plasma concentrations in the clinical range, among medication compliant patients.

The pharmacokinetic profile of oral naltrexone has a sawtooth pattern of peaks and troughs with each daily dose. Side effects generally correspond to peak dose effect. One solution to this less than optimal profile was the development of injectable extended release naltrexone, which provides therapeutic levels for 30 days after a single injection [37]. King and colleagues [38] suggest that individuals who show greater naltrexone biotransformation, thus higher levels of urinary 6-β-naltrexol experience more side effects.

The safety and tolerability of naltrexone was initially established in opioid-dependent patients two decades before it was approved by the FDA for alcohol dependence [39]. Subsequently, Croop and colleagues published a multicenter 12-week, open-label safety report on naltrexone in the treatment of alcoholism which provided further support to the notion that naltrexone is generally well-tolerated with transient side-effects [40]. In their study (500 naltrexone treated patients and 238 patients in a similar un-medicated reference group), the most frequently reported adverse effects were: nausea (9.8%), headache (6.6%), dizziness (4.4%), nervousness (3.8%), fatigue (3.6%), anxiety (2%), and depression (1.4%). Suicidal ideation or attempts occurred in less than 1% of the participants. Croop points out that the reports of depression and suicidal ideation are difficult to associate with naltrexone because psychiatric comorbidity is highly prevalent in alcohol-dependent samples. Specifically, the suicide risk is highly increased in co-morbid cases of alcoholism and major depressive disorder. A recent review estimates that the lifetime risk for suicide among alcohol-dependent samples is eight percent [41], and there is no indication that naltrexone treatment increases that risk.

In the Croop *et al*. study, naltrexone was discontinued in 15% of the participants, with nausea being the most common reason for medication discontinuation [40]. One commonly used clinical strategy to mitigate side effects and improve retention in treatment is starting the oral naltrexone dose at 25 mg, half the typical target dose, for one to several days before increasing the dose to the standard clinical dose (50 mg/day). A review of multiple studies comparing the tolerability of oral versus injectable extended-release formulation by Roozen and colleagues found that the drop-out rates varied between 20 and 32% of patients on injectable naltrexone, and that between 36 and 50% of patients prescribed oral naltrexone discontinued treatment after 12 weeks [37].

Naltrexone does not have hepatotoxic effects at the recommended dose of 50 to 100 mg per day. Historic investigations with high doses of naltrexone such as 300 mg per day reported a significant increase in hepatic enzymes [42-44]. However, a review of the literature by Brewer and Wong [45] concluded that in patients treated for heroin or alcohol addiction, there is no evidence that naltrexone causes clinically significant liver disease or exacerbates serious pre-existing liver disease. Co-morbid liver

diseases such as cirrhosis or viral hepatitis are common among alcohol-dependent patients, therefore it is recommended that patients treated with naltrexone have baseline and follow-up tests of liver function [45]. The side-effect profile of injectable extended-release formulation is similar to that of oral naltrexone. However, the injections may result in pain, tenderness, swelling, redness of skin (erythema), bruising, or itching (pruritus) at the injection site. Infrequently, more severe injection site reactions occur including hardening of soft tissue in the skin (induration), inflammation of connective tissue (cellulitis), hematoma, abscess, sterile abscess, and necrosis. While rare, some of these cases are known to require surgical treatment.

## NALTREXONE IN CLINICAL PRACTICE

Despite the FDA approval of oral naltrexone in 1994 and of the injectable extended-release formulation in 2006, clinicians have been slow to adopt medication for alcoholism. Delays in diffusion of scientific innovation into community practice may have initially played a role, despite the availability of training materials for professionals provided by federal agencies. Clearly, a multitude of factors played a role in the slow dissemination of naltrexone's findings from science to practice. One factor is that traditionally, the bulk of community addiction treatment consists of psychosocial interventions provided by non-medical counselors who may not advocate or be aware of naltrexone. Some counselors and physicians providing addiction treatment have a bias against medication and define abstinence as a medication-free state. Even physicians who specialize in treating addiction often describe barriers to prescribing naltrexone including the cost and concerns about side effects, compliance or efficacy. Extended-release injectable naltrexone assures compliance for one month; however, it is less likely to be covered by insurance and the out-of-pocket cost is often prohibitive for many patients.

An additional concern cited by some physicians is that continued use of naltrexone is associated with an up-regulation of opioids receptors leading to an opioid supersensitivity, necessitating special considerations for pain management. If opioid treatment becomes necessary for an elective procedure, naltrexone therapy can be discontinued for 2 or 3 days, and the opioid can then be given in conventional doses. However, if opioids are needed for pain management in someone with recent naltrexone ingestion, or on the extended-release preparation, pain relief can still be obtained but at higher than usual opioid doses with close medical monitoring to override the blockade. The opioid analgesic action needs to be titrated to avoid respiratory depression or over-sedation. It is therefore recommended that patients carry safety identification cards providing information about naltrexone and instructions for treatment in the event of an emergency. In sum, a number of issues have been cited as barriers in the translation of naltrexone from the laboratory to the clinic. A critical next step in the field of addiction treatment involves the effective dissemination of scientific findings, including pharmacotherapy clinical trials, to practice.

## COMPLIANCE AND PERSISTENCE

A plausible explanation for some inconsistencies in the literature concerning naltrexone efficacy may be due to complicating issues of medication compliance and persistence, which is of significant concern to healthcare providers and researchers alike. A retrospective database analysis by Kranzler *et al.* [46] found that only 14.2% of a large, multi-site outpatient population with alcohol-related claims persisted in seeking 80% of prescription refills for naltrexone throughout the 6-month treatment period. Findings on naltrexone compliance vary widely depending on the setting and sample. In an alcohol-dependent outpatient study, 66% of patients were compliant while also concurrently enrolled in a 12-week rehabilitation program [47]. Another study involving treatment-seeking alcohol-dependent individuals found compliance rates to be at 71% with the use of the Medication Event Monitoring System during a 12-week period [48]. Likewise, Cramer *et al*. [49] reported 71% compliance among alcohol-dependent outpatients randomized to a 13-week medication condition; however, compliance dropped to 43% for those randomized to the long-term, 52-week naltrexone condition. This comparison shows that compliance rates over longer periods of naltrexone treatment are less promising. These findings also suggest that compliance is highest among those who meet DSM-IV criteria for alcohol dependence and actively seek treatment for this disorder.

To address low compliance with oral naltrexone, several approaches have been developed to monitor and facilitate compliance in clinical trials, such as electronic monitoring devices like Medication Event Monitoring System and Electronic Drug Exposure Monitor caps, pill counts, and self-reports [31, 48]. However, these tools to enhance compliance in research studies are rarely, if ever, implemented in clinical practice. Though undoubtedly useful, the validity of these mechanisms is at a disadvantage, as they depend on subjective accounts or bottle opening data to account for compliance. Since its introduction to the market, the appeal of the injectable extended-release form of naltrexone is its convenient once-a-month dose administration. Compliance data are more reliable, being verified by in-person physiological receipt of naltrexone and is accounted for by the mode of administration, which requires interaction with a healthcare provider.

In a systematic comparison of the efficacy and tolerability of oral versus injectable naltrexone, Roozen *et al.* [37] found that the injectable formulation demonstrated equal or greater benefits as oral naltrexone in promoting total abstinence, time to first drink, and a reduction in the event rate of heavy drinking days compared to placebo. However, oral naltrexone was reported to be more effective in lowering relapse rates and number of heavy drinking days compared to placebo, whereas no significant results were found for injectable naltrexone [37]. In a 24-week placebo-controlled study of alcohol-dependent individuals, compliance rates were reported to be 63 to 65% for all 6 injections and 72% for at least 4 injections [50]. Although these rates cannot be directly compared to oral naltrexone compliance data due to different assessment points, the 13-week and 52-week time points in Cramer's study suggest compliance rates for injectable naltrexone are comparably higher [49]. Injectable naltrexone compliance is affected by adverse injection site events, though overall, less side effects are reported than for oral naltrexone [37]. These injection site events are unique to the injectable formulation (discussed in detail above). Inconsistencies in compliance data may be the result of variances in study design, duration of treatment, and means of assessment. Nevertheless, efforts to enhance compliance with naltrexone treatment are essential to ensure patients have the best chance of benefiting from this pharmacotherapy in their efforts to reduce or stop drinking.

## NEUROBIOLOGICAL MECHANISMS

Alcohol dependence is a complex disorder resulting from the interplay between biological and psychosocial factors [51, 52]. While several neurotransmitter systems are activated by alcohol administration, the literature on neurobiology of addiction has focused on the role of mesolimbic dopamine as central to the stimulatory and reinforcing effects of alcohol [53, 54]. Studies have found that both alcohol consumption and alcohol cue exposure prior to drinking increase dopamine activity in the nucleus accumbens (NAC), suggesting that prior learning and anticipation of reinforcement activates a dopamine response that is isomorphic to the effect of alcohol on mesolimbic dopamine activation [55]. An important question that has only been partially answered is how alcohol might influence mesolimbic dopamine activity.

The opioidergic system has also been associated with the pathophysiology of substance use disorders, including alcoholism

[56-58]. Opioid receptors are putatively involved in the rewarding properties of several substances, such as opiates, cocaine, and alcohol [57, 59]. Alcohol is thought to produce some of its reinforcing effects through the release of endogenous opioids in certain brain areas and through interactions with the dopaminergic system, particularly in the midbrain. More specifically, researchers have suggested that alcohol consumption triggers the release of endogenous opiates, which in turn may mediate mesolimbic dopaminergic activity [60, 61]. The release of endogenous opiates is also thought to inhibit γ-amino-butyric acid interneurons, which subsequently release dopaminergic neurons from inhibition [62]. Naltrexone is an opioid receptor antagonist which has highest affinity for μ-opioid receptors, and may act selectively for those types of receptors [63]. Naltrexone is thought to exert some of its effects *via* antagonism of midbrain dopaminergic activity through endogenous opioids. This notion is consistent with a study demonstrating that ethanol administration increased dopamine activity in the NAC and that naltrexone administration reduced alcohol-induced dopaminergic activity in the NAC [64].

Although naltrexone has highest affinity for μ-opioid receptors, research has shown that naltrexone binds, in a dose-dependent manner first the μ-receptor, then the δ-opioid receptor, and finally with the κ-opioid receptor [65, 66]. In fact, a PET study suggested that at a dose of 50 mg/day, naltrexone produces nearly complete (approximately 90%) blockade of μ-opioid receptors [34, 35], compared to 20 to 35% blockage of δ-opioid receptors [67], and presumably lower occupancy of κ-opioid receptors. More recently, a PET study of μ- and δ-opioid receptor blockade in naltrexone-treated alcohol-dependent subjects by Weerts *et al.* [36] revealed that 50 mg of naltrexone was sufficient to produce 95% inhibition of μ-opioid receptors but only 21.1% inhibition of δ-opioid receptors in various brain regions of interest. Further, there was significant variability across subjects [36]. The authors concluded that further investigation of the relationship between individual differences in δ-opioid receptor blockade by naltrexone and clinical outcomes should be conducted. This approach is consistent with the realization that activity at a single receptor is insufficient for modulating multiple targets for the treatment of complex psychiatric disorders, such as alcoholism [68]. Together, these results suggest that attention should also be paid to κ- and δ-opioid receptors when examining responses to naltrexone and its dose response curve. To that end, Gianoulakis and De Waele [69] have proposed that stimulation of μ- and δ-opioid receptors was associated with the positive reinforcing effects of alcohol, whereas stimulation of the κ-opioid receptor mediated the aversive effects of alcohol in animal models. In addition, recent preclinical work has suggested that the dynorphin system is up-regulated in alcohol-dependent states, producing a negative affective state that may promote drinking *via* negative reinforcement [70, 71]. In fact, a preclinical study found that blockade of κ-opioid receptors with nor-binaltorphimine selectively decreased alcohol self-administration in ethanol-dependent animals [72]. To that end, it is plausible to hypothesize that naltrexone-induced blockade of κ-opioid receptors may contribute to its clinical effects through amelioration of the up-regulated dynorphin state during alcohol dependence.

Animal studies have also shown that naltrexone consistently reduces alcohol consumption and palatability in rats [73, 74]. A recent study has suggested that δ-opioid receptors are involved in taste-reactivity to ethanol and consumption in rats [75], although the authors concluded that multiple opioid receptors mediate those responses. Taken together, these studies highlight the multiple systems underlying the pharmacological and biobehavioral effects of alcohol and naltrexone, including multiple opioid receptors, which are the primary targets of naltrexone. As suggested by Gelernter *et al*., naltrexone may be particularly well suited for pharmacogenetic analyses, in part because its neuroreceptor targets, and genes coding them, are well characterized. The pharmaco-genetics of naltrexone for the treatment of alcoholism are discussed in more detail below.

## BIOBEHAVIORAL MECHANISMS

Pharmacotherapies for alcoholism can have beneficial effects on drinking outcomes through a variety of biobehavioral mechanisms. Putative mechanisms of action of naltrexone include the following:

A. *Reduction of Alcohol Cravings/Urge to Drink.* Medications may reduce drinking by dampening urges to drink. Alcohol craving has been examined in many contemporary models of alcoholism [76, 77]. As demonstrated by Monti and colleagues [78, 79], 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. Medications that dampen urge to drink hold promise for promoting abstinence and reducing alcohol consumption. Several studies have shown that naltrexone reduces urge to drink, as compared to placebo [19, 80].

B. *Blunting of the Stimulatory Effects of Alcohol.* A medication may reduce alcohol intake by blunting the rewarding and stimulant effects of alcohol, which in turn may not promote abstinence per se, but may be useful in reducing the likelihood that a "slip" drinking episode may result in heavy drinking and perhaps help prevent a full-fledged relapse. This mechanism may be particularly salient in the effects of naltrexone on drinking outcomes [80-82]. Pharmaco-therapies that blunt the rewarding and stimulatory effects of alcohol upon consumption may be useful in decreasing relapse and frequency of heavy and harmful drinking, and this appears to be one of the prominent mechanisms of action of naltrexone [83, 84].

C. *Potentiation of the Sedative and Unpleasant Effects of Alcohol*. A medication may reduce drinking by increasing the likelihood that drinking will lead to alcohol-induced sedation, which is marked by unpleasant and dysphoric feelings such as: down, heavy-headed, sluggish, inactive, and sedated (items from the Biphasic Alcohol Effects Scale) [85]. Studies have shown that naltrexone causes an increase in self-reported fatigue, tension, and confusion [86] and blunts alcohol's effects on tension reduction during the descending limb of intoxication [87], when the sedative effects of alcohol are most salient [85, 88].

D. *Increasing Cognitive Control*. Recent pre-clinical data have suggested that pharmacotherapies, including naltrexone, may work by increasing cognitive control and decreasing impulsive decision-making [89, 90]. A recent human laboratory study using a delayed discounting task found that acute doses of naltrexone (50 mg) reduced impulsive choice among individuals with an external attribution style [91]. This study, however, did not examine impulsive decision-making in the context of alcohol intoxication, which is highly relevant as naltrexone is thought to interact with the effects of alcohol upon consumption. Clearly, further investigation of the neurocognitive effects of naltrexone on response inhibition, particularly during alcohol administration, seems warranted.

Several laboratory-based studies have sought to elucidate the biobehavioral mechanisms of action of naltrexone, primarily by examining the effects of naltrexone on subjective responses to alcohol. Results of such studies revealed that naltrexone dampens feelings of alcohol-induced stimulation [81, 82], decreases ratings of liking of the alcohol [29], causes an increase in self-reported fatigue, tension, and confusion [86], reduces alcohol consumption,

and slows down the progression of drinking in a delayed access laboratory paradigm [92]. A study by King *et al*. [86] found that individuals with a family history of alcohol dependence showed greater naltrexone-induced attenuation of the stimulatory effects of alcohol. More recently, pre-clinical [89] and human laboratory [91] studies have suggested that naltrexone may work by decreasing impulsive decision-making.

In short, laboratory-based studies have improved our understanding of the biobehavioral mechanisms of action of naltrexone, yet dose-response studies are scarce. To date, only three studies have examined the dose-dependent effects of naltrexone [29-31] with results suggesting a benefit of 100 mg/day over 50 mg/day in decreasing "liking of the alcohol" [29] and reducing drinking in laboratory paradigms, but only among individuals with a positive family history [30]. These findings suggest that the dose of naltrexone may be targeted on the basis of individual differences, although neither study examined the role of genetic moderators. Future studies may advance the literature by comparing multiple doses of naltrexone in order to empirically test the most efficacious dose of naltrexone on its putative clinical mechanisms of action. Importantly, a dose-response study of naltrexone has substantial advantages for examing moderators of medication response that could ultimately lead to a more targeted and efficacious use of naltrexone through individualized dose prescription.

## GENETIC PREDICTORS OF MEDICATION RESPONSE

The field of pharmacogenetics focuses on identifying genetic factors that account for variability in pharmacotherapy effects, both in terms of pharmacodynamics and efficacy [93]. The field has grown rapidly and has greatly benefited from advances in molecular genetic tools for identifying gene polymorphisms, developments in bioinformatics and functional genomics, and from findings from the human genome project [93, 94]. The goal of this line of research is to optimize drug therapy by identifying genetic factors that predict who is more likely to respond to certain pharmacotherapies. Genetic factors can account for individual differences in drug toxicity and efficacy in many ways. For instance, genetic variability may lead to differences in drug metabolism and disposition through functional differences in enzyme activity or drug transporters. Alternatively, genetic polymorphisms may impact a drug's target, such as a particular receptor.

Efforts to identify genetic variants that may moderate the effects of naltrexone have focused on the gene coding for μ-opioid receptors (i.e., OPRM1 gene), which represent the primary target of naltrexone [95, 96]. One of the most widely studied polymorphisms of the OPRM1 gene is the +118A/G single neucleotide polymorphism (SNP) located in the +118 position in exon 1, which codes for the Asn40Asp substitution (rs1799971). Molecular studies of this polymorphism initially suggested that the A (i.e., Asn40) to G (i.e., Asp40) substitution affects receptor affinity for endogenous ligand β-endorphin leading to a gain in function, such that the Asp40 variant was thought to bind β-endorphin with greater affinity than the Asn40 allele [59]. However, a more recent study of the functional significance of this SNP suggested that the Asp allele has deleterious effects on both mRNA and protein yield, leading to a loss of function, rather than a gain [97]. Several studies have tested the relationship between the Asn40Asp SNP of the OPRM1 gene and substance use disorders, particularly alcoholism and opioid dependence. The results, however, are inconsistent and while some investigations have found support for the association between this SNP and alcohol or opioid dependence [98-101], several studies have failed to replicate these associations [102-108].

The inconsistent findings between this functional polymorphism and the diagnostic phenotype of alcohol or drug dependence suggest that perhaps searching for more narrowly defined phenotypes may result in more consistent, and perhaps more useful, results [109-111]. To that end, the Asn40Asp SNP of the OPRM1 gene has been associated with a differential response to opioid antagonists in clinical trials of naltrexone [95, 112] and in laboratory studies of naloxone [113, 114]. Oslin *et al*. [95] found that this SNP was associated with clinical response to naltrexone among alcohol-dependent patients, such that individuals with at least one copy of the Asp40 allele, coding for more potent μ-opioid receptors, reported lower relapse rates and longer time to return to heavy drinking when treated with naltrexone, as compared to individuals who were homozygous for the wild-type (Asn40) allele. These findings have been recently replicated and extended in the Combining Medications and Behavioral Interventions for Alcoholism study [112], which found that carriers of the Asp40 allele receiving Medication Management (MM) showed a significant decrease in heavy drinking days, as compared to homozygotes for the Asn40 allele. In addition, 87% of carriers of the Asp40 allele had a good clinical outcome to naltrexone + MM, as compared to 55% of homozygotes for the Asn40 allele; and the groups did not differ in their response to MM plus placebo [112]. These results have been subjected to a haplotype-based analyses which largely confirmed the role of the functional Asn40Asp SNP [115]. However, a recent study did not find support for the moderating role of Asp40 allele on the pharmacogenetics of naltrexone for alcoholism in a sample of male veterans [116]. In addition to the focus on the μ-opioid receptor (ORPM1) gene, the study by Gelernter *et al*. [116] examined multiple polymorphisms in the genes coding for μ (OPRM1; located in chromosome 6), κ (OPRK1; located in chromosome 8), and δ (OPRD1; located in chromosome 1) opioid receptors. This study examined three markers in the OPRM1 gene (including the Asn40Asp SNP), one marker in the OPRK1 gene, and three markers in the OPRD1 gene in a reanalysis of clinical outcomes in the Veterans Affairs Cooperative Study 425 "Naltrexone in the Treatment of Alcohol Dependence". Results did not support the role of the Asn40 SNP of the OPRM1 gene as a moderator of clinical responses to naltrexone, yet there was some support for the role of a marker in the OPRK1 gene (SNP rs963549) in predicting relapse rates. In discussing these results, Gelernter and colleagues suggested that measures of drinking behavior may not be precise enough for pharmacogenetic analyses, particularly when assessed through recall methods [116]. Further research may address this methodological consideration by refining phenotypic measures.

An intermediate-phenotype driven placebo-controlled laboratory study of naltrexone by Ray and Hutchison [80] found that carriers of the Asp40 allele of the OPRM1 gene showed significantly greater naltrexone-induced blunting of alcohol "high," as compared to individuals who were homozygous for the Asn40 allele. These findings suggest that the differential clinical response to naltrexone, discussed above, may be due to differential blunting of the subjective experience of alcohol reward as a function of genotype. In other words, these results advance a biobehavioral mechanism that may account for this important clinical pharmacogenetic effect. Additional studies are certainly needed to probe for this relationship before individualized treatment approaches may be implemented. Translational approaches have the potential to inform clinical practice by identifying individuals who are more likely to benefit from a given pharmacotherapy on the basis of genetic factors.

## PSYCHOSOCIAL PREDICTORS OF RESPONSE

In addition to identifying genetic determinants of clinical response to naltrexone, several studies have examined psychosocial moderators of outcome. Both are equally important efforts as identification of the responder may not require genetic testing should psychosocial variables be identified. Psychosocial predictors of clinical response to naltrexone examined to date include the following:

A. *Gender*. The majority of findings on gender differences in naltrexone treatment response suggest that men report

greater medication effects than women [30, 87, 117]. When examining the effects of naltrexone during the descending limb of the blood alcohol concentration, Ray *et al*. [87] found a significant main effect of gender, both in reports of greater alcohol-induced stimulation as well as naltrexone-induced decrease of stimulatory effects of alcohol in male subjects. Likewise, in a 6-month placebo-controlled study examining the efficacy and tolerability of injectable naltrexone, Garbutt *et al*. [117] found a significant treatment effect in alcohol-dependent males, but none in females. Interestingly, only a handful of studies report greater treatment response in women, although these findings were limited to immediate effects after isolated drinking events, rather than effects on drinking behavior over an extended period of time [118].

B. *Age*. Baros *et al*. [48] found older subjects to be more naltrexone-compliant, as determined by electronic monitoring and urinary riboflavin analysis. Among the most compliant group, who were significantly older than non-compliers, Baros *et al*. [48] reported better treatment outcomes such as more days of abstinence, less heavy drinking days, and less total standard drinks for the treatment period. Though not statistically significant, the older, and more compliant patients, also reported lower drinks per drinking days, more days to first drink and first heavy drinking day [48]. Analysis of demographical differences between persistent and non-persistent subjects in another large multi-site outpatient trial also showed that the probability of naltrexone-persistence increased by 3% with each additional year in age [46]. As treatment efficacy is highly dependent on medication compliance, age may predict who may be targeted for naltrexone therapy and have better treatment outcomes but the effects of age on outcome may be fully mediated through medication compliance.

C. *Family history of alcoholism*. Several studies have suggested that individuals with a positive family history for alcoholism may benefit most from naltrexone [119-121]. Family history positive individuals reported greater time between first and second drinks [118] and lower total number of drinks consumed [30], compared to individuals with family history negative for alcoholism. By definition, family history of alcoholism is confounded with genetic etiology and may ultimately not have enough specificity as a marker of treatment response to naltrexone.

D. *Psychiatric co-morbidity and alcohol typology*. Numerous studies have examined the association between psychiatric co-morbidity and naltrexone efficacy. This is especially relevant in light of the high co-morbidity rates among alcohol-dependent individuals [122]. Studies have shown that alcohol-dependent subjects with antisocial traits [121] and other substance use disorders [119] have better clinical response to naltrexone while other studies have not supported an association between co-morbidity and clinical outcomes [123, 124]. Although it is not clearly established whether co-morbidity is a reliable and useful predictor of clinical response, naltrexone was found to be safe and effective among dually-diagnosed individuals, such as patients with post-traumatic stress disorder [125], schizoaffective disorder, schizophrenia, and bipolar disorder [126]. Although studies have examined the differential effectiveness of various pharmacotherapies for alcohol dependence as a function of alcohol typology, few studies have employed this approach to predicting naltrexone response. One such study used Babor's typology to classify research participants into one of two categories: "Type A," which is characterized by later onset of alcohol pathology, fewer childhood risk factors, less psychopathology and fewer substance abuse symptoms, or "Type B," which is characterized by early onset, greater childhood risk factors, positive family history for alcoholism, and more co-morbid psychopathology [127, 128]. They found that treatment outcomes for naltrexone, in the context of psychosocial interventions, were significantly better among Type A alcohol-dependent individuals across the following three outcomes: percent heavy drinking days, percent days abstinent, and drinks per day [127]. This suggests that naltrexone may be most beneficial among Type A individuals, who are characterized by late onset and less severe drinking problems. However, these results are inconsistent with previous results suggesting that naltrexone may be most effective among individuals with earlier age of onset of alcohol dependence, which is comparable to Babor's "Type B" individuals, although this study employed a different set of criteria for characterizing their research participants [119].

## LIMITATIONS AND FUTURE DIRECTIONS

Although naltrexone is a well-established and widely researched treatment for alcohol dependence, several critical questions remain about how this medication can be optimally used. In light of the generally small effect size of naltrexone for the treatment of alcoholism [84], efforts to improve its clinical usefulness have focused on identifying treatment responders *via* psychosocial and, more recently, genetic markers [129]. While these initial results have been encouraging, particularly for the Asn40Asp SNP of the OPRM1 gene, considerable work remains to be done before these findings can inform clinical practice. For instance, studies have shown that the allele frequencies for the Asn40Asp SNP of the OPRM1 gene varies as a function of ethnicity [103], hence pharmacogenetic studies of naltrexone must carefully consider ethnicity for this genetic locus and, more broadly, in the context of personalized medicine [130, 131]. Additional clinical questions regarding the optimal length of treatment, ideal dosage, and psychosocial predictors of treatment response may also inform clinical practice. Lastly, the effective translation of addiction science into practice represents a major and crucial step in ensuring that patients suffering from alcohol use disorders receive empirically-supported treatments and that these treatments are more widely available.

## ACKNOWLEDGEMENTS

LAR would like to acknowledge funding for her research from ABMRF, the Foundation for Alcohol Research, and from the National Institute on Alcohol Abuse and Alcoholism (NIAAA).

## ABBREVIATIONS

| | | |
|---|---|---|
| FDA | = | Food and Drug Administration |
| PET | = | Positron emission tomography |
| MEMS | = | Microelectromechanical systems |
| NAC | = | Nucleus accumbens |
| SNP | = | Single nucleotide polymorphism |
| MM | = | Medication Management |

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**Received: October 23, 2009** **Revised: December 14, 2009** **Accepted: December 18, 2009**