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Pharmacogenetics of Naltrexone And Disulfiram in Alcohol Dependent, Dually Diagnosed Veterans

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Abstract

Background—We explored pharmacogenetic interactions in subjects from a medication treatment study for alcohol dependence in subjects with co-occurring mood, anxiety, and psychotic disorders.

Methods—Alcohol dependent (AD) subjects received naltrexone alone, placebo alone, disulfiram with placebo or disulfiram with naltrexone. They were genotyped for *OPRM1* rs1799971 (Asn40Asp), and *DBH* rs1611115 (C-1021T). N=107 male European-American subjects were included.

Results—There were no significant interactions with *OPRM1*. *DBH* interacted with naltrexone on the primary outcome of abstinence from heavy drinking, ($X^2(1)=5.23$, $p=0.02$). “T” allele carriers on naltrexone had more abstinence compared to “CC” subjects on naltrexone. “T” allele carriers on naltrexone had the highest overall rates of abstinence from heavy drinking (>90%). Also, *DBH* genotype interacted with disulfiram ($p=0.01$) on drinks per drinking day with less drinking for subjects with the “CC” genotype than for T allele carriers on disulfiram.

Conclusions—*DBH**rs1611115*T associated with better response to naltrexone, while for those on disulfiram that drank, “CC” subjects drank less than T carriers.

Scientific Significance—Genotyping rs1611115 may be useful in understanding inter-individual differences in AD treatment response.

Future Directions—Further study of rs1611115 pharmacogenetics is warranted.

Keywords

Pharmacogenetics; alcohol dependence; alcohol treatment; dual diagnosis

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BACKGROUND AND OBJECTIVES

Disulfiram and oral naltrexone are two of the four U.S. Food and Drug Administration (FDA) approved medications for treating alcohol dependence (AD). There is significant variation in treatment response to medications for AD including naltrexone.¹⁻³ Previous studies have shown that response to medication treatments for AD may vary based on a patient's individual genetic background (review, Arias and Sewell,⁴). Research into pharmacogenetic interactions may help to personalize and optimize the response to medications.

Several trials have examined the association between variation in opioidergic genes such as the gene encoding the mu-opioid receptor (*OPRM1*) and treatment response to opioid receptor antagonists such as naltrexone for alcohol dependent subjects, with conflicting results.⁴ Much of the focus in these studies has been on the potential interaction between medication and a particular functional single nucleotide polymorphism (SNP) in *OPRM1* located in exon 1 (rs1799971) with regard to treatment response. Despite the clear functionality of rs1799971, and the fairly strong evidence of a pharmacogenetic effect, this effect may not by itself be sufficiently strong to be clinically significant.

There are no previous reports of pharmacogenetic analyses for disulfiram in *prospective, controlled*, alcohol treatment clinical trials. However there is one recent pharmacogenetic study reporting on disulfiram in a retrospective analysis of clinical data. Mutschler et al.,⁵ reported no effect of the genotype on clinical response to supervised disulfiram in a small retrospective analysis from a specialized clinical program. However they did find an increased risk of side effects for carriers of the variant “T” allele for a potential candidate SNP near the gene encoding dopamine beta-hydroxylase *DBH*, rs1611115 (C-1021T), that appears to be functional.⁶⁻⁸ There is also an association between persons homozygous for the variant “T” allele and increased cocaine-induced paranoia, and a recent report of better response to disulfiram treatment for cocaine dependence with the CC genotype.^{9,10}

Finding the right combination of medications to treat patients with cooccurring AD and major Axis I disorders such as Major Depression is an even more difficult task for clinicians than treating AD alone. A pharmacogenetic approach may help to devise a method to match patients to a more ideal regimen, eventually augmenting the current diagnosis-based strategy. However, to date there are no studies performed in primarily dual diagnosis (DDx) alcohol dependent populations testing pharmacogenetic hypotheses in subjects with cooccurring substance dependence and other Axis I disorders.

We sought to evaluate clinically significant pharmacogenetic interactions with functional genetic variants in loci that are physiologically relevant to the mechanism of action of naltrexone and disulfiram in DDx subjects with alcohol dependence. A subset of genotyped participants from a randomized clinical trial evaluating naltrexone, disulfiram, the combination, or no medication, in DDx, alcohol dependent subjects were included in this study. Based on the previous studies we hypothesized that the G allele of rs1799971 would be associated with a better response to medication treatment on drinking outcomes. We also

hypothesized that the rs611115 variation would be associated with a better response to medication treatment on drinking outcomes.

METHODS

Subjects and Recruitment

The detailed methods of the parent study from which this pharmacogenetic sample is derived have been published previously.¹¹ The study was approved by the Human Subjects Subcommittee of Yale University, the VA Connecticut Healthcare System and the Northampton and Bedford, Massachusetts VAs, which are all affiliated with the New England Mental Illness Research and Education Clinical Center (MIRECC). The original trial sample (n=254) consisted of outpatients from the MIRECC-affiliated clinics who met criteria for a current DSM IV major Axis I disorder *and* alcohol dependence, determined by structured clinical interview,¹² who were abstinent no more than 29 days, and provided written informed consent. Subjects were also required to be abstinent for 3 days prior to randomization and to agree to strive for a goal of complete abstinence.

The present sample consists of N=109 European American subjects that gave written informed consent for not only the treatment trial, but for genotyping, and that provided a blood sample for DNA. The analysis was restricted to European Americans, which avoids potential confounding by population stratification and the complex gene-gene interactions due to having subjects with different ancestry. Only two subjects were female, so they were removed from the analysis to avoid confounding based on sex, leading to the final sample of n=107 subjects.

Treatments

Two-hundred fifty-four subjects were randomized to one of four groups for the original 12-week trial. Groups included; (1) naltrexone alone; (2) placebo alone; (3) disulfiram and naltrexone; or (4) disulfiram and placebo. The naltrexone condition was blinded with a placebo control, but the disulfiram condition was open-label. All subjects also received weekly Clinical Management/Compliance Enhancement therapy¹³ administered by trained research personnel.

Assessments

Primary assessments for the parent study were measures of alcohol use as measured by the Timeline Follow-Back Interview¹⁴ at each weekly visit to collect a detailed self-report of daily alcohol and substance use throughout the 84-day treatment period as well as retrospectively for the 90 day pre-treatment period prior to randomization.

Genotyping

DNA was extracted from whole blood using standard methods. Of the SNPs examined, *OPRM1*: rs1799971 is a functional variant as discussed above, and the *DBH* SNP rs611115 (C-1021T), is putatively functional. Both SNPs were genotyped using TaqMan fluorogenic 5' nuclease assays (Livak et al., 1995) and the ABI PRISM 7900 Sequence Detection

System (ABI, Foster City, CA, USA). At least 8% of genotypes were repeated for quality control, with complete concordance.

Statistical Methods

We evaluated main effects and interactions of genotype and treatment on two primary drinking variables: abstinence from heavy drinking, and drinks per drinking day. We chose abstinence from heavy drinking because previous studies have found a significant pharmacogenetic effect on this outcome measure, and it is currently the preferred FDA benchmark outcome. We chose the outcome of drinks per drinking day because it is a sensitive measure in subjects that continue to drink during a study. A heavy drinking day was defined as more than four standard drinks in a day. Abstinence from heavy drinking was defined as having no days of heavy drinking while in the active treatment period. Data were checked for normality prior to analysis and log-transformation was applied to “drinks per drinking day.” The binary outcome of abstinence from “heavy drinking” was analyzed using logistic regression. The continuous outcome “drinks per drinking day” was analyzed using linear regression. We used alpha level of 0.025 to correct for testing two independent SNPs on each outcome measure. Since there were only single subjects at certain combinations of levels of the predictor variables (disulfiram, naltrexone, and genotype) and each outcome, we could not reliably assess three-way interactions. Only models with all possible two-way interactions (between disulfiram, naltrexone, and genotype) were considered. The effects of *OPRM1* and *DBH* variants were tested in separate models. Exact tests were used for the post-hoc comparisons of the binary outcome abstinence from heavy drinking. All analyses were performed in SAS 9.3.

RESULTS

Descriptive statistics

A total of 107 European American males were included in the analysis. Descriptive demographics for subjects are shown in Table 1. Two-thirds of subjects had a lifetime history of Major Depressive Disorder, and 37% had a lifetime history of PTSD. The concomitant psychotropic medication use rate was high, especially Selective Serotonin Reuptake Inhibitors (65%) and anticonvulsants (39%). The average baseline number of heavy drinking days and drinking days out of the previous 30 days for the subjects are also shown in Table 1. There were no significant differences in baseline drinking measures compared across medication groups.

There were no genotype deviations from Hardy-Weinberg Equilibrium expectations when tested for the entire sample and for each medication group separately. For 107 subjects, the minor allele frequency of rs611115 (C-1021T) was .23, and for rs1799971 (A118G) was .1.

Drinking Outcomes

Abstinence from heavy drinking

We performed a logistic regression analysis on the dichotomous indicator of heavy drinking (1= any days with heavy drinking in the 84 study days, 0 = abstinence from heavy drinking).

OPRM1 results for abstinence from heavy drinking

There was only a significant main effect of disulfiram in the *OPRM1* model ($X^2(1)=3.86$, $p=0.05$), but no interaction with genotype for either medication.

DBH results for abstinence from heavy drinking

92 subjects with available genotype and drinking data were included in this model. There was a significant interaction between *DBH* rs1611115 and naltrexone ($X^2(1)=5.23$, $p=0.02$, see Table 2a). There was *higher* rate of abstinence from heavy drinking for subjects on naltrexone than for those not on naltrexone when the *DBH* genotype was “T” allele carrier (17 out of 18, 94.4% vs. 14 out of 20, 70.0%) but a *lower* rate for subjects on naltrexone compared to those not on naltrexone when the *DBH* genotype was “CC” (15 out of 26, 57.7% vs. 22 out of 28, 78.6%). Using Fisher's Exact Test, there is a significantly higher rate of naltrexone-treated subjects carrying the “T” allele who were abstinent from heavy drinking compared to CC subjects (Fisher's Exact Test, $p=.01$, see Figure 1). Among placebo-treated subjects, there was no difference in rates of abstinence from heavy drinking when compared by genotype (Fisher's Exact Test, $p=.5$).

Mean number of drinks per drinking day

This variable was log-transformed to better approximate normality and a general linear model was used for analysis. Twenty-four of the subjects had values for this variable, since only 24 subjects drank during the active treatment period and were genotyped for the *DBH* SNP.

OPRM1 results for mean number of drinking days

There were no significant effects in the *OPRM1* model, which included all main effects and two-way interactions of both medications, but not the three-variable interaction (genotype by disulfiram by naltrexone) due to the small number of subjects on both medications.

DBH results for mean number of drinks per drinking day

There was a significant interaction between disulfiram and naltrexone ($F(1,17)=7.35$, $p=0.01$) and a significant interaction between *DBH* rs1611115 and disulfiram ($F(1,17)=7.52$, $p=0.01$, Table 2b, Figure 2). Within the group of subjects not randomized to naltrexone, the mean number of drinks per drinking day was *lower* on disulfiram than not on disulfiram ($p=0.12$); for those on naltrexone the mean was *higher* on disulfiram than not on disulfiram ($p=0.04$).

DISCUSSION

The results of this study do not support a pharmacogenetic interaction with the *OPRM1* SNP rs1799971 and naltrexone or disulfiram on drinking related outcomes in this sample of dually diagnosed alcohol dependent males. This is consistent with our previous study that failed to find a naltrexone-*OPRM1*-treatment interaction in a larger sample.¹⁵ There were two significant interactions with the *DBH* rs1611115 SNP that withstand correction for multiple comparisons: (1) subjects who were treated with naltrexone that carry the variant

“T” allele reported greater abstinence from heavy drinking than subjects with the “CC” genotype: (2).there was a greater reduction in drinks per drinking day with disulfiram in subjects with the “CC” genotype. While the disulfiram- *DBH* rs1611115 SNP interaction should be interpreted cautiously, it is a novel finding that suggests further research with this SNP. Due to the small sample size, these results should be considered preliminary, and need to be replicated.

The finding of better response to naltrexone with *DBH* rs1611115 SNP is novel and intriguing. In “T” allele carriers, those on naltrexone had almost a 25% higher rate of abstinence from heavy drinking than those on placebo, almost a 40% higher rate than those homozygous for “CC” on naltrexone, and almost a 16% greater rate than those with CC genotype on placebo. Among naltrexone-treated subjects, a significantly greater proportion of “T” allele carriers were abstinent from heavy drinking than CC subjects, a finding that, together with the significant effect of genotype at the level of the logistic regression model, suggests a real and potentially clinically significant pharmacogenetic effect. Notably, the “T” allele carriers on naltrexone had excellent outcomes with a >90% abstinence from heavy drinking rate, but the CC genotype subjects on naltrexone appear to have a trend towards worse outcome than placebo. Thus, this SNP may differentiate not just those that will have a better response to the medication, but may help identify those that will actually do worse on naltrexone than not on the medication. These preliminary results for *DBH* rs1611115 suggest that it may be relevant to personalized treatment. Another recent pharmacogenetic analysis of alcoholism treatment found broadly analogous results in that there was an interaction with medication, genotype and age of onset for alcoholism for which some subjects did better on placebo than active medication. In a clinical trial of sertraline treated alcohol dependent subjects, those homozygous for the long (L') allele of the 5-HTTLPR polymorphism of *SLC6A4* did better on sertraline if they had late onset alcoholism, but better on placebo if they had early onset alcoholism.¹⁶

DBH rs1611115 genotype has an effect on plasma dopamine beta-hydroxylase enzyme levels in European Americans regardless of whether they are alcoholic, but detoxified alcoholics also exhibit decreased plasma levels of the enzyme compared to healthy controls independent of genotype.¹⁷ However, compared to subjects with the CC genotype, subjects with the T variant allele may have a subjectively different reward system in terms of basal norepinephrine and dopamine levels, the effects of norepinephrine on dopaminergic transmission in the nucleus accumbens, and behavioral effects of medications that are active in the ventral striatum and prefrontal cortex.¹⁸ We might speculate that AD subjects carrying the variant *DBH**T allele may have an addiction-prone phenotype of excessive alcohol and reward seeking which is attenuated by naltrexone.^{8,19} CC subjects could experience exacerbation of the protracted abstinence syndrome from naltrexone leading to a worse outcome than with placebo treatment. We emphasize that this is speculation based on preliminary data.

The interaction between *DBH* and disulfiram is probably not clinically significant based on these results, especially since the best disulfiram outcome (the CC subjects on disulfiram) was essentially the same as the best nondisulfiram group (the T allele subjects not on

disulfiram); these findings should be interpreted cautiously and should likely be explored further.

The lack of significant findings for the naltrexone-*OPRM1* rs1799971 interaction are contrary to those of Anton et al.,²⁰ who reported a better clinical response to naltrexone in individuals who were the G allele carriers. Though the allele frequency for the “G” allele was at that expected for a European American sample, our study was underpowered (N=106).

A major strength of this study is that it is the first pharmacogenetic analysis in a primarily “real world” DDx population of alcohol dependent subjects. Limitations include that subjects were enrolled in a complicated study that included treatment with both naltrexone and disulfiram, subjects included in the analysis had a heterogeneous group of psychiatric diagnoses, and were prescribed various psychotropic medications for their Axis I conditions. We did not use co-occurring diagnoses or concomitant medications as covariates in the statistical analysis because the small sample size and the high variation in cooccurring diagnoses made it infeasible to have a meaningful statistical control for these conditions. The results of the study should be interpreted cautiously because of the small sample size.

SCIENTIFIC SIGNIFICANCE AND FUTURE DIRECTIONS

Our findings are similar to other recent studies suggesting that dopaminergic system related genetic variants may interact with naltrexone and disulfiram. In the future, it may be necessary to use methods of combining information from SNPs at various genetic loci (especially dopaminergic genes), to accurately predict medication treatment response. Further study of pharmacogenetic interactions with *DBH* rs1611115 in both treatment trials and laboratory settings is warranted.

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FIGURE 1.

The genotype by medication interaction is significant in the logistic regression model ($p=.02$). Post-hoc comparison is significant ($p=.01$) within the naltrexone group. A total of $N=92$ subjects were included in this comparison.

FIGURE 2.

The genotype by medication interaction is significant in the general linear model ($p=.01$), the post-hoc tests are marginally significant ($p=.06$). $N=24$ subjects were included in this comparison.

Variables	N= 107
Demographic Variables	
	<i>mean, sd</i>
Age	47.6, 8.1
Education years	12.7, 2.0
Gender	<i>n, %</i>
Male	107, 100
Race	
Caucasian	107, 100
Marital Status	
Single	25, 23.4
Married/Living with partner	13, 12.1
Widowed/Divorced/Separated	68, 63.5
Clinical Variables	
Axis I Diagnosis-Lifetime [*]	
Major Depressive Disorder	66, 61.7
Post Traumatic Stress Disorder	37, 34.6
Other Anxiety Disorders	32, 29.9
Bipolar Type Disorders	19, 17.8
Schizophrenia Type Disorders	10, 9.3
Cocaine Dependence	51, 47.7
Opiate Dependence	14, 13.1
Medication ^{**}	
Anticonvulsants	39, 36.5
Benzodiazepines	1, 0.9
Lithium	7, 6.5
Atypical Antipsychotics	5, 4.7
Typical Antipsychotics	19, 17.8
SSRI Antidepressants	65, 60.7
Tricyclic Antidepressants	4, 3.7
Other Antidepressants	48, 44.9
Other Anxiolytics	6, 5.6
Baseline Drinking	
	<i>mean, sd</i>
# of drinking days out of last 30 days	16.1, 12.1
# of heavy drinking days out of last 30 days	14.9, 12.2

* Participants may have more than one diagnosis

** Participants may be on more than one medication

Table 2

a. and b.

a. Results for <i>DBH</i> rs1611115 (C-1021T) on Abstinence from Heavy Drinking (N=92)			
Logistic Regression	df	Wald Chi-Square	p-value
<i>DBH</i>	1	2.35	0.1
Disulfiram	1	0.90	0.3
<i>DBH</i> *Disulfiram	1	0.45	0.5
Naltrexone	1	0.51	0.5
<i>DBH</i> *Naltrexone	1	5.23	0.02*
Disulfiram*Naltrexone	1	0.72	0.4

b. Results for <i>DBH</i> rs1611115 (C-1021T) on Drinks Per Drinking Day (N=24)		
Effect	F Value *	Pr > F
<i>DBH</i>	0.1	0.8
Disulfiram	0.26	0.6
<i>DBH</i> *Disulfiram	7.52	0.01*
Naltrexone	0.3	0.6
<i>DBH</i> *Naltrexone	0.51	0.5
<i>Disulfiram</i> *Naltrexone	7.35	0.01*

Degrees of freedom are 1 and 17 for each of the effects in the model.

* significant at p<0.025 level, 92 subjects included in this model

* significant at p<0.025 level, 24 subjects included in this model