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COMT Val158Met, BDNF Val66Met, and OPRM1 Asn40Asp and Methamphetamine Dependence Treatment Response: Preliminary Investigation

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Methamphetamine (MA) dependence is a significant source of deleterious consequences to individual and public health including HIV infection, psychological distress, and cardiovascular disease. No medications have been approved for MA dependence and response to behavioral therapy is variable. The identification of genetic markers for MA dependence treatment response could have significant utility via the identification of responsive sub-groups as well as the biological processes underlying variability in treatment response. Yet no studies have examined potential genetic markers of response to treatment for MA dependence.

We performed an exploratory study examining potential associations between three well described single nucleotide polymorphisms (SNPs) with putative involvement in MA dependence, catechol-O-methyltransferase (COMT) Val158Met, brain-derived neurotrophic factor (BDNF) Val66Met, and the mu opioid receptor (OPRM1) Asn40Asp polymorphisms, and treatment outcome among participants of a randomized, double-blind, placebo-controlled trial of modafinil, with contingency management and cognitive behavioral therapy, for MA dependence. Treatment outcome was assessed via Treatment Effectiveness Score (TES, mean MA-negative urine drug screens during treatment), a standard indicator of treatment outcome in MA dependence. Of 71 participants in the main trial ¹, four African American and 2 Asian participants were excluded to avoid issues related to population stratification and four participants did not consent to DNA collection leaving 61 Non-Hispanic Caucasians (referred to as Caucasians) and Hispanic Caucasians (Hispanics) who were genotyped for the three SNPs.

We examined main effects for genotype, as well as potential medication by genotype interactions, on TES using t tests and linear regression models among Hispanics and Caucasians separately. Cohen's effect size (*d*) for genotype and medication effects by genotype were also calculated. To maximize power, participants with Val/Val genotype were compared to Met carriers (Val/Met or Met/Met genotype) for COMT Val158Met and BDNF Val66Met and participants with AsnAsn genotype were compared to Asp carriers (Asn/Asp or Asp/Asp genotype) for OPRM1 Asn40Asp.

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Hispanics were significantly ($p < 0.05$) younger (mean age 32.7 years, standard deviation 8.2, minimum 19.6, maximum 46.0) relative to Caucasians (mean age 43.2 years, standard deviation 9.9, minimum 23.3, maximum 64.8) but there were no significant differences in age, gender, or baseline methamphetamine use by genotype for any of the three SNPs. Genotype frequencies did not differ from those expected under Hardy-Weinberg equilibrium.

There was a significant main effect for BDNF Val66Met on TES among Caucasians ($p = 0.039$; Table), but not Hispanics, with mean TES significantly higher among Val/Val Caucasians relative to Caucasian Met carriers. The effect size for BDNF Val66Met on TES in Caucasians was large ($d = 0.78$). There were no significant main effects of COMT Val158Met or OPRM1 Asn40Asp on TES in either ethnicity although effect sizes for the Met allele of COMT Val158Met in Hispanics and the Asp allele of OPRM1 Asn40Asp in Caucasians were in the moderate range (Table).

There was a significant genotype by medication interaction for COMT Val158Met among Hispanics ($p = 0.009$; Table), with TES significantly higher and a large effect size for modafinil relative to placebo among participants with Val/Val genotype but not among Met carriers. All six Caucasian Val/Val participants were in the placebo group and therefore a medication by COMT Val158Met interaction could not be assessed in Caucasians. There were no significant genotype by medication interactions for BDNF Val66Met or OPRM1 Asn40Asp in either ethnicity.

Results of this study must be interpreted considering the study's limitations. This was an exploratory study aimed at providing preliminary data on the pharmacogenetics of response to treatment for MA dependence and results require replication in prospective studies and additional samples. Participants were genotyped retrospectively following a clinical trial and therefore findings may be due to chance. Finally, the small cell sizes for comparisons by genotype and genotype by medication interactions provide limited power to detect statistically significant differences and precluded employment of a Bonferroni correction for multiple comparisons or a genome wide significance level. Despite these limitations, we know of no previous studies examining genetic markers of MA dependence treatment response and therefore results of this study are important for guiding the design of future pharmacogenetic studies of MA dependence. We provide effect size estimations for genotype effects on treatment outcome with these future studies in mind.

We found a significant main effect for BDNF Val66Met genotype on treatment outcomes in MA dependence with worse outcomes among Caucasian Met carriers. The BDNF Val66Met Met allele is associated with reduced neuronal activity-dependent BDNF secretion, deficits in memory and hippocampal function², and lower subjective response to amphetamine³ which may affect response to treatment for MA dependence. In particular, altered memory function among Met carriers may interfere with efforts to quit MA with the cognitive behavioral platform provided in this study. If future studies confirm worse outcomes in Met carriers, then medications targeting the BDNF signaling pathway and TrkB, the BDNF receptor, may be candidates for treating MA dependence, particularly in carriers of the Met allele.

There were no significant main effects for COMT Val158Met or OPRM1 Asn40Asp on treatment outcome, although effect sizes were moderate for the COMT Val158Met Met allele in Hispanics and the OPRM1 Asn40Asp Asp allele in Caucasians. Reduced COMT function, higher prefrontal cortex dopamine levels⁴, and better cognitive performance associated with the COMT Val158Met Met allele⁵ could result in improved outcomes in Met carriers. In alcohol dependence, the OPRM1 Asn40Asp Asp allele is associated with

altered stress responsivity, increased subjective response to alcohol, and lower rates of relapse to heavy drinking with naltrexone treatment ⁶ while a haplotype containing OPRM1 Asn40Asp, but not OPRM1 Asn40Asp alone, was associated with subjective response to amphetamine ⁷. Putative reductions in mu opioid receptor function with the Asp allele may result in increased ability to quit MA similar to the case with naltrexone treatment in alcoholism. Future studies should examine MA dependence treatment outcomes and these SNPs in adequately powered clinical samples.

The interaction between modafinil and COMT Val158Met observed in our study of MA dependence is similar to findings from a study of cognitive effects of modafinil in healthy sleep deprived adults which also found response to modafinil only among Val/Val participants ⁸. The Val allele is associated with lower prefrontal dopaminergic and cognitive function relative to the Met allele ^{4, 5}. Response to modafinil, a medication with dopaminergic and cognitive enhancing effects, may be limited to Val/Val participants who experience a deficit in dopaminergic and cognitive functioning relative to Met carriers that is ameliorated by treatment with modafinil. Additional studies examining COMT Val158Met as a potential marker of response to modafinil, as well as other dopaminergic and cognitive enhancing medications, in stimulant dependence are warranted.

Although results of this exploratory study are preliminary, they provide the first data on potential genetic moderators of MA dependence treatment response and may guide the design of future prospective pharmacogenetic studies in MA dependence.

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Table
Treatment effectiveness score (TES) and Cohen's effect size (*d*) for genotype and medication by genotype among methamphetamine dependent participants

Non-Hispanic Caucasians							Hispanic Caucasians		
Genotype Main Effect									
	N	TES Mean (SEM)	d	N	TES Mean (SEM)	d			
COMT Val158Met									
Val/Val	6	12.0 (6.5)	---	14	8.2 (2.2)	---			
Met Carriers	29	15.3 (2.5)	0.22	12	14.9 (3.7)	0.54			
BDNF Val66Met									
Val/Val	23	18.1 (3.0) *	0.78	18	10.6 (2.2)	- 0.08			
Met Carriers	12	8.3 (3.1) *	---	8	11.5 (4.9)	---			
OPRM1 Asn40Asp									
Asn/Asn	25	13.1 (2.7)	---	20	10.9 (2.3)	---			
Asp Carriers	10	18.8 (4.4)	0.41	6	11.0 (5.4)	0.01			
Genotype by Medication Interaction									
COMT Val158Met									
Val/Val	Modafinil	0	N/A	N/A	6	14.0 (3.6) **	1.46		
	Placebo	6	12.0 (6.5)	---	8	3.9 (1.5) **	---		
Met Carriers	Modafinil	17	15.5 (3.4)	0.04	6	8.5 (1.6)	- 0.93		
	Placebo	12	14.9 (3.8)	---	6	19.5 (6.6.)	---		
BDNF Val66Met									
Val/Val	Modafinil	10	22.0 (4.6)	0.49	9	12.7 (2.6)	0.44		
	Placebo	13	15.1 (3.8)	---	9	8.6 (3.6)	---		
Met Carriers	Modafinil	7	6.3 (2.7)	- 0.40	3	7.0 (0.6)	- 0.57		
	Placebo	5	11.0 (6.7)	---	5	14.2 (7.9)	---		
OPRM1 Asn40Asp									
Asn/Asn	Modafinil	11	17.0 (4.2)	0.52	9	11.9 (2.6)	0.19		

		Non-Hispanic Caucasians			Hispanic Caucasians		
		N	TES Mean (SEM)	d	N	TES Mean (SEM)	d
Asp Carriers	Placebo	14	10.0 (3.5)	---	11	10.0 (3.6)	---
	Modafinil	6	12.8 (6.2)	- 1.34	3	9.3 (2.6)	- 0.23
	Placebo	4	27.8 (2.1)	---	3	12.7 (11.7)	---

* $p < 0.05$ for BDNF Val55Met genotype after controlling for age, gender, baseline methamphetamine use, and medication treatment group

** $p < 0.01$ for modafinil versus placebo after controlling age, gender, and baseline methamphetamine use