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

To the Editors:

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 use via the identification of responsive subgroups 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 3 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. The 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] 4 African American and 2 Asian participants were excluded to avoid issues related to population stratification, and 4 participants did not consent to DNA collection, leaving 61 non-Hispanic whites (referred to as whites) and Hispanic whites (Hispanics) who were genotyped for the 3 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 whites 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.

Hispanics were significantly ($P < 0.05$) younger (mean [SD] age, 32.7 [8.2] years; range, 19.6–46.0 years) relative to Caucasians (mean [SD] age, 43.2 [9.9] years; range, 23.3–64.8 years), but there were no significant differences in age, sex, or baseline methamphetamine use by genotype for any of the 3 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 whites ($P = 0.039$; Table 1) but not Hispanics, with mean TES significantly higher among Val/Val whites relative to white 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 whites were in the moderate range (Table 1).

There was a significant genotype by medication interaction for COMT Val158Met among Hispanics ($P = 0.009$; Table 1), 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 6 white Val/Val participants were in the placebo group; and therefore, a medication by COMT Val158Met interaction could not be assessed in whites. 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 the treatment for MA dependence, and the results require replication in prospective studies and additional samples. Participants were genotyped retrospectively after 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 use of a Bonferroni correction for multiple comparisons or a genomewide 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 white Met carriers. The BDNF Val66Met Met allele is associated with reduced neuronal activity-dependent BDNF secretion, deficits in memory and hippocampal function,[2] and lower subjective response to amphetamine,[3] 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 whites. Reduced COMT function, higher prefrontal cortex dopamine levels,[4] and better cognitive performance associated with the COMT Val158Met Met allele[5] 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] whereas 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

TABLE 1. Treatment Effectiveness Score (TES) and Cohen's Effect Size (*d*) for Genotype and Medication by Genotype Among Methamphetamine-Dependent Participants

	Non-Hispanic Whites			Hispanic Whites		
	No. Participants	TES, Mean (SEM)	*d*	No. Participants	TES, Mean (SEM)	*d*
Genotype main effect						
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
Placebo	14	10.0 (3.5)	—	11	10.0 (3.6)	—
Asp carriers						
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 Val66Met genotype after controlling for age, sex, baseline methamphetamine use, and medication treatment group.
†$P < 0.01$ for modafinil versus placebo after controlling age, sex, and baseline methamphetamine use.

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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AUTHOR DISCLOSURE INFORMATION

The authors declare no conflicts of interest.

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Treatment of Indiscriminate, Inappropriate Sexual Behavior in Frontotemporal Dementia With Carbamazepine

To the Editors:

Although not the most common behavioral problem among demented individuals, inappropriate sexual behavior is consistently rated as one of the most difficult to manage[1,2] and frequently leads to institutionalization.[3] There is a paucity of controlled studies addressing treatment of inappropriate sexual behavior in dementia; most published pharmacologic strategies involve efforts to globally reduce libido.

Inappropriate sexual behavior may arise by several mechanisms. Neuropathologically, it may be a manifestation of the general disinhibition that occurs with damage to the lateral orbitofrontal circuit of the frontal/subcortical system.[4–6] Probably less commonly, inappropriate sexual behavior may be seen with bilateral amygdala lesions, as a symptom of the Klüver-Bucy syndrome (KBS)[7,8]; in their original primate studies, Klüver and Bucy[9] described this inappropriate sexual behavior as indiscriminate, with affected monkeys attempting to copulate with same-sex monkeys, other species, and even inanimate objects. Inappropriate sexual behavior may also rarely arise from hypothalamic lesions as in Klein-Levin syndrome.[4,5] Finally, inappropriate sexual behavior may be a manifestation of preexisting functional psychopathology such as mania or paraphilia.[5]

Frontotemporal dementia (FTD) is a histopathologically heterogeneous condition that generally affects frontal and anterior temporal cortexes.[10] Thus, it is not surprising that both behavioral disinhibition and KBS symptoms can be seen in these patients,[10] both of which may lead to inappropriate sexual behavior. We describe a patient with FTD and inappropriate sexual behavior, in whom discriminating between these 2 types of inappropriate sexual behavior led to successful targeted pharmacologic treatment with carbamazepine.

CASE REPORT

A 78-year-old man has had progressive dementia with memory loss, abulia, poor hygiene, and urge incontinence for 3½ years. Initially, there were no significant behavioral problems; nor was there any evidence of depression or psychosis. His medical history was significant only for essential hypertension treated with atenolol and for vitamin B12 deficiency, treatment of which antedated the dementia. There was no family history of dementia or any history of alcohol use. On examination, he was a cooperative, euthymic but profoundly bradyphrenic man with prominent perseveration and mild echolalia. Speech was underproductive but otherwise neurologically intact. He was disoriented, and his memory was impaired; but confrontation naming, comprehension, ideomotor praxis, and calculations were spared. He was severely echopractic on contrasting programs, and Luria recursive figures were perseverative and stimulus bound. Laboratory work was unrevealing; a magnetic resonance imaging scan showed severe focal atrophy of the frontal and anterior temporal lobes.

The patient's presentation was felt to be most consistent with FTD. He was placed in a community nursing home where he initially did well. However, after approximately 4 months, he gradually became increasingly hypersexual, making verbal and sometimes physical sexual advances toward staff and patients. Remarkably, these sexual advances were made toward both females and males (there was no evidence of a prior homosexual or bisexual orientation). The inappropriate sexual behavior failed to respond to behavioral measures or to the selective serotonin reuptake inhibitor paroxetine, 40 mg/d.

The diagnosis of FTD and the indiscriminate nature of his inappropriate sexual behavior were strongly suggestive of the Klüver-Bucy syndrome, although there was no hyperphagia or hyperorality; he was rather docile, but this may have been consistent with his premorbid personality. Paroxetine was discontinued, and carbamazepine was started and titrated to a maximum dosage of 800 mg/d, attaining a serum drug concentration of 6.0 mg/L (therapeutic concentration, 4–12 mg/L). Within several days of attaining a therapeutic concentration, the sexual behavior completely abated and never recurred over the subsequent 6 months, at which time he was lost to follow-up.

DISCUSSION

In treating this patient, we felt a need to differentiate truly indiscriminate sexual behavior from simply disinhibition of his usual sexual interests and behaviors. Whereas it is conceivable that he may have had a lifelong covert sexual interest in men, this seemed highly unlikely, and we suspect that the sexual behavior was indeed a KBS symptom.

There are unfortunately few published cases of treatment of inappropriate sexual behavior with carbamazepine, and no controlled studies. Whereas it has been suggested that carbamazepine may be useful for behavioral disinhibition,[11] this has been mostly in the context of physical aggression; and there is only one published case report of its use in dementia with sexual disinhibition.[12] In contrast, there are several reports of its use in various symptoms of KBS,[7,13,14] although not specifically targeting the sexual symptoms.

In managing inappropriate sexual behaviors in dementia, one must first take a comprehensive history regarding current symptoms, as well as a history of sexual interests and behaviors. It must also be kept in mind that certain behaviors in patients with dementia may seem to be sexually motivated but may in fact be a manifestation of other things such as disorientation, a desire for affection, or genitourinary discomfort. First-line treatment of inappropriate sexual behaviors will generally be nonpharmacologic, including providing a tolerant environment, redirecting behavior,