CONSENSUS ARTICLE

COMT Val158Met modulates subjective responses to intravenous nicotine and cognitive performance in abstinent smokers

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The catechol-O-methyltransferase (COMT) Val158Met polymorphism may be a risk factor for nicotine addiction. This study examined the influence of the COMT Val158Met polymorphism on subjective, physiological and cognitive effects of intravenous (IV) nicotine use in African Americans (AAs; n = 56) and European Americans (EAs; n = 68) smokers. Overnight abstinent smokers received saline followed by 0.5 and 1.0 mg per 70 kg doses of nicotine, administered 30 min apart. Smokers with valine (Val)/Val genotype, compared with methionine (Met) carriers, had greater negative subjective effects from IV nicotine and had more severe withdrawal severity following overnight abstinence from smoking. Women with Val/Val genotype reported greater difficulty concentrating and irritability than men with Val/Val or Met carrier genotypes. The Val/Val genotype was associated with better performance on the math task and in AA smokers it was associated with greater systolic blood pressure. These results support the rationale of pharmacologically inhibiting COMT to aid with smoking cessation among Val/Val genotype smokers.

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INTRODUCTION

Catechol-O-methyltransferase (COMT) is an enzyme that inactivates dopamine (DA), epinephrine and norepinephrine as well as tightly regulating DA in the prefrontal cortical areas.1-3 The gene encoding COMT contains a well-studied single-nucleotide polymorphism that results in the presence of methionine (Met) or valine (Val) at codon 108 (in s-COMT) or codon 158 (in m-COMT).4 The Val-coded allele is three to four times more active than the Met-coded allele, resulting in reduced DA levels in the synapse.5,6 The COMT Val158Met variation has been widely researched for many phenotypes of psychiatric disorders including depression,7 psychosis8 and drug addiction.9 Given the key role of DA in mediating drug reward, drug-seeking, and withdrawal states, studying the COMT Val158Met variation is especially important for addictive disorders, including nicotine addiction.10

A recent meta-analysis concluded that the Val/Val genotype may be a risk factor for developing nicotine addiction.9 Although some studies reported an association between the Val/Val genotype and poor response to smoking cessation treatments,11-13 other studies did not confirm these results, and some studies reported opposite findings.14,15 Surprisingly, only a few studies have investigated the potential mechanism by which the COMT Val158Met polymorphism may modulate the risk for and treatment response to nicotine addiction. In a functional magnetic resonance imaging study, abstinent smokers with the Val/Val genotype performed worse on the n-back test, which measures working memory.16 Furthermore, abstinent smokers with the Val/Val genotype had greater blood flow increases in brain areas associated with cigarette craving.17 These findings suggest that smoking cessation may be particularly difficult for smokers with the Val/Val genotype. However, systematic studies examining the COMT Val158Met polymorphism on withdrawal severity and nicotine responses are lacking. Such studies may provide better insight into the mechanisms of the observed COMT Val158Met effects on nicotine dependence.

The goal of this study was to determine the influence of the COMT Val158Met polymorphism on nicotine responses in smokers. The outcomes examined were those predicted to be likely modulated by the COMT enzyme, including measures of cognitive performance, withdrawal severity, subjective drug effects and cardiovascular responses to nicotine.18-21 To assess the outcomes of interest, we used an intravenous (IV) nicotine administration procedure. In contrast to other slower nicotine delivery systems, IV nicotine administration produces rewarding effects in male and female smokers.22 Based on the known biological effects of the COMT Val158Met variant, we hypothesized that smokers who carry two copies of the Val allele would experience less rewarding effects from nicotine, perform worse on selected cognitive tasks and experience more severe withdrawal symptoms compared with those who carry the Met allele.

MATERIALS AND METHODS

Subjects
We recruited 124 non-treatment-seeking cigarette smokers in and around New Haven, CT through newspaper advertisements and flyers. All participants were between 18 and 50 years old and smoked between 10 and 25 cigarettes per day during the past year. The study sample included 100 smokers that were described in a previous study23 as well as 24 additional smokers. The demographics are shown in Table 1.

The participants were medically healthy and did not have current active medical problems (including hypertension) and were not on any current prescription medications. Potential participants were excluded if they were dependent on alcohol or any drugs other than nicotine, as determined by...
measures included blood pressure (systolic and diastolic) and heart rate. These measures were taken during the medication treatment and in the experimental sessions at 5, 1, 2, 3, 5, 8, 10 and 15-min intervals following the saline or nicotine deliveries. Plasma cortisol measurements were taken at baseline, before each of the three injections and at the end of the session. Plasma cortisol has been shown to be sensitive to nicotine administration and abstinence from nicotine.29–32 Studies also suggest that the COMT Val158Met polymorphism may influence cortisol release in response to stress or drugs of abuse.33,34

The subjective measures included the Drug Effects Questionnaire (DEQ), the Brief Questionnaire on Smoking Urges (BQSU), the Minnesota Nicotine Withdrawal Scale (MNWS) and the Positive and Negative Affect Schedule (PANAS). The MEDEQ was used to measure subjective responses to IV nicotine and consisted of 10 items: drug strength, high, feel stimulated, good effects, bad effects, anxious, sedated, feel down, want more drug and like drug. Smokers rated each item on a visual analog (Likert) scale, from ‘not at all’ to ‘extremely.’ The DEQ was given at 1, 3, 5, 8, 10 and 15 min after the saline and nicotine administration. The BQSU is a 10-item scale originally developed by Tiffany and Drobes.15,36 Smokers were asked how strongly they agreed or disagreed with items on a seven-point Likert scale. This scale has been found to be highly reliable in reflecting nicotine deprivation levels.37,38 The MNWS measures withdrawal symptoms from tobacco and includes items to assess cigarette craving, irritability/anger, anxiety, difficulty concentrating, restlessness, increased appetite, depressed or sad mood, and insomnia. The PANAS was a 20-item scale that assesses both positive and negative affective states.41 The BQSU, MNWS and PANAS were administered before and after the session.

Cognitive testing was measured using the Mathematical Processing (MP) task, the Running Memory Continuous Performance Test (CPT) and the Stroop Test within the Automated Neuropsychological Assessment Metrics computer package, a computer-administered cognitive battery of performance tests developed by the Department of Defense.42 As the main cognitive outcome measure, we used the throughput score, which combines response speed, accuracy and consistency, and reflects cognitive efficiency.42 The MP, CPT and Stroop assessments were chosen for their sensitivity to acute nicotine administration.43,44

Nicotine administration
Nicotine bitartrate was acquired from Interchem (Manchester, CT, USA). A research pharmacist at the VA CT Healthcare System prepared the nicotine samples. A total volume of 5 ml containing either 0.5 mg or 1 mg per 70 kg of nicotine, was injected IV over a 30-s interval via a catheter located in an antecubital vein, and the baseline measures for the study sample

| Table 1. Baseline measures for the study sample |
|------------------------------------------------|
| COMT genotype | Overall | Met | Val/Val | P- value |
|---------------|---------|-----|---------|----------|
| (n=68)        | (n=34)  |     | (n=44)  |          |
| Sex (male/female) | 90/34  | 59/21 | 31/13 | NS |
| Age, years    | 37.4 (8.5) | 37 (8.7) | 39 (8.1) | NS |
| Race (AA/EA)  | 56/68  | 31/49 | 25/19 | 0.05 |
| Body mass index | 28.9 (5.5) | 28.3 (5.3) | 30.1 (5.8) | NS |
| FTND          | 5.5 (2.1) | 5.2 (2.2) | 6.1 (2.0) | 0.02 |
| Cigarettes per day | 18.7 (12.2) | 18.5 (14.2) | 19.1 (7.4) | NS |
| Years of smoking | 16.7 (4.5) | 16.6 (4.5) | 16.9 (4.5) | NS |
| 3’HC/cotinine | 0.38 (0.03) | 0.41 (0.033) | 0.33 (0.04) | NS |
| Nicotine (ng ml⁻¹) | 3.1 (3.3) | 3.3 (0.37) | 2.77 (0.50) | NS |
| Heart rate    | 67.5 (10.4) | 68.0 (10.9) | 66.5 (9.4) | NS |
| Systolic blood pressure | 116.4 (12.4) | 115 (12.2) | 119 (12.7) | NS |
| Diastolic blood pressure | 68.2 (7.0) | 67.3 (70) | 69.9 (7.1) | 0.05 |

Abbreviations: AA, African American; COMT, catechol-O-methyltransferase; EA, European American; FTND, Fagerstrom Test for Nicotine Dependence; Met, methionine; NS, nonsignificant; Val, valine; 3’HC, 3’-hydroxycotinine, 3’OHC, 3’-hydroxycotinine.

the Structured Clinical Interview for DSM-IV44 and verified by urine drug screening. Written informed consent was obtained from each participant before study participation. The IV nicotine experimental sessions were conducted in the Biostudies Unit located at the West Haven campus of the VA Connecticut Healthcare System. The participants were compensated for their participation. This research protocol was approved by the Yale and VA Connecticut Healthcare System Human Subjects Subcommittees.

Procedure
Following an overnight abstinence from smoking, the participants arrived at the outpatient clinic at approximately 8:00 am for the experimental session, which lasted about 3 h. Abstinence from smoking was confirmed by measuring expired carbon monoxide (CO; <10 parts-per-million). The baseline measures for the study sample

Nicotine administration
Nicotine bitartrate was acquired from Interchem (Manchester, CT, USA). A research pharmacist at the VA CT Healthcare System prepared the nicotine samples. A total volume of 5 ml, containing either 0.5 mg or 1 mg per 70 kg of nicotine, was injected IV over a 30-s interval via a catheter located in a forearm vein. The nicotine doses administered were within the range of nicotine delivered by smoking one cigarette. Our prior research demonstrated that these doses produced robust physiological and subjective responses in male and female smokers.22 The injections were given 30 min apart, which allowed subjective and cardiovascular responses to return to baseline levels.22–24

The genotyping was conducted after the experimental sessions were completed using a blinded method.

Dependent measures
Outcome measures assessed biochemical, physiological, subjective and cognitive domains. Biochemical measures included CO, plasma nicotine, cotinine and 3’-hydroxycotinine. The plasma nicotine concentrations and expired CO were used to confirm the overnight abstinence from smoking. Plasma cotinine concentrations were used as a measure of prior nicotine exposure.28 Expired CO, plasma nicotine, 3’-hydroxycotinine and cotinine measurements were taken before the experimental session. Physiological measurements included blood pressure (systolic and diastolic) and heart rate.
manufacturer’s protocol (Illumina, San Diego, CA, USA). Genotypes were called using BeadStudio software (Illumina).

Data analysis
Study outcomes were analyzed with a repeated-measures model using the Statistical Analysis System (SAS), version 9.2 (Cary, NC, USA). As a result of the small number of smokers (n = 22) with Met/Met genotype, we combined Met/Met group with Met/Val and compared this combined group with the Val/Val group, similar to previous studies on COMT and cigarette smoking.30,50 For blood pressure, heart rate and the DEQ, multiple assessments were collected for each saline and nicotine dose. For these outcomes, the model included the COMT rs4680 genotype (Val/Val vs Val/Met or Met/Met), nicotine dose (saline, 0.5 and 1 mg per 70 kg), sex (male vs female), race (African-American (AA) vs Caucasian), nicotine metabolite ratio, body mass index, and interaction terms including genotype × dose, genotype × race and genotype × sex. In previous studies, race, sex, body mass index, and nicotine metabolite ratio (NMR) have been shown to modulate nicotine’s pharmacological effects.30,50 For the NWSC, BQSU, PANAS and cognitive measures, the assessments were completed at the beginning and end of the session. For these outcomes, the model included time of measurement (pre- vs post-session), rather than the dose. Significant main effects were followed by post hoc testing. Genotypes for AA and European-American (EA) groups were consistent with Hardy–Weinberg equilibrium expectations (EA: χ² (1) = 0.56, P = NS; AA: χ² (1) = 0.70, P = NS). Values of P < 0.05 in two-tailed tests were considered statistically significant unless otherwise specified.

Subjects were classified as genetically AA or EA on the basis of the ancestry informative markers panel, using the program STRUCTURE v 2.3.2.1.51 as described previously.24 Among the subjects included in this study, two subjects reporting to be of AA descent clustered in the EA group, and two subjects reporting to be EA clustered in the AA group. Adjusting for the degree of admixture did not significantly change our results on the influence of COMT Val158Met variation on the study outcomes.

RESULTS
Physiological
The systolic blood pressure, diastolic blood pressure and heart rate responses were dose dependent such that responses to 1.0 mg nicotine > 0.5 mg nicotine > saline (all P-values < 0.0001; Figure 1). Significant findings for heart rate, and systolic and diastolic blood pressure are summarized in Table 1 and Figure 1. The body mass index was not significant for heart rate or blood pressure. The NMR values were positively correlated with the nicotine-induced heart rate and systolic blood pressure (P < 0.01).

Subjective
For all the DEQ assessments, the rating for the 1.0 mg nicotine or 0.5 mg nicotine does were greater than for saline (all P-values < 0.05). For the rating of ‘stimulated,’ ‘high,’ ‘feel drug strength,’ the ratings for the 1.0 mg nicotine > 0.5 mg nicotine (P < 0.05). The NMR values were positively correlated with the ratings of ‘stimulated’ ‘high,’ and ‘feel anxious’ (P < 0.05). The results for the DEQ items are summarized in Table 1 and Figure 2. The results for withdrawal severity, as measured by MNWS and BQSU, are summarized in Table 2 and Figure 3. The NMR values were positively correlated with the MNWS and BQSU factor 1 scores (P < 0.05). For the PANAS, neither a main effect of genotype nor a genotype × session interaction was found to influence positive and negative affect states (P > 0.05).

Cognitive
As expected, the MP, CPT and Stroop Test performances at the end of the session were better than they were at baseline (P < 0.0001). The results of the cognitive assessments are summarized in Table 3.

Cortisol
Plasma cortisol measurements did not show significant main effects for genotype or genotype × time interactions (P > 0.05).

DISCUSSION
We found that smokers with the Val/Val genotype, compared with the Met carriers, had greater negative subjective effects from IV nicotine and more severe withdrawal severity following overnight abstinence from smoking. Women with the Val/Val genotype reported greater difficulty concentrating and irritability than men with the Val/Val or Met allele containing genotypes. The Val/Val

Figure 1. Mean ± s.e.m. of (a) heart rate (b) systolic and (c) diastolic blood pressure as functions of catechol-O-methyltransferase (COMT) genotype and nicotine dose. Mean ± s.e.m. of (d) heart rate (e) diastolic blood pressure as functions of COMT genotype and sex and (f) systolic blood pressure as functions of COMT genotype and race. NIC, nicotine.
genotype was associated with better performance on the math task and in AA smokers, it was associated with greater systolic blood pressure readings. These findings are consistent with most of our hypotheses regarding COMT Val158Met polymorphism effects on nicotine responses.

In our study, smokers with the Val/Val genotype, compared with Met carriers, reported higher ratings of mostly negative drug effects, including ‘feel anxious,’ ‘feel bad effects,’ ‘feel sedated,’ ‘feel down’ and ‘feel the drug strength.’ In contrast, no genotype effects were observed for the ratings of items that reflect nicotine’s reinforcing properties including ‘good drug effects,’ ‘like the drug effects’ or ‘want more drug.’ This genotype effect was primarily observed in response to nicotine, and not to saline, administration, suggesting a pharmacogenetic effect of the Val/Val genotype. COMT effects were observed for both 0.5 and 1.0 mg per 70 kg of nicotine dose. Previous studies have shown that COMT Val158Met variation moderates responses to non-drug rewards or aversive stimuli, however, the influence of the COMT Val158Met polymorphisms on the rewarding or aversive drug effects has not been reported. For example, healthy controls with the Val/Val genotype report a decreased ability to experience reward in the routine of daily life and report less happiness compared with those with the Met/Met genotype. In a recent functional magnetic resonance imaging study healthy controls with the Val/Val genotype had greater activation of amygdala in response to fearful/angry facial stimuli. Our findings extend these studies further by demonstrating that COMT Val158Met variation may also moderate subjective drug responses to nicotine.

Consistent with the DEQ findings, we found that smokers with the Val/Val genotype had greater withdrawal severity following an
overnight abstinence, as measured by the MNWS and the BQSU. Further analysis of the individual MNWS items showed that smokers with the Val/Val genotype had greater craving, more difficulty concentrating and more irritability than Met carriers. To our knowledge, these findings are the first to demonstrate that the COMT Val158Met variation moderates withdrawal severity in smokers. In a previous study, smokers with the Val/Val genotype had greater blood flow to prefrontal cortical regions that are associated with cigarette craving on abstinence from smoking.17 More severe withdrawal in smokers with the Val/Val genotype may have important treatment implications (see below).

The Val/Val genotype was associated with faster reaction time in the math test but did not influence the performance on the CPT and Stroop tasks. In contrast to our findings, a functional magnetic resonance imaging study revealed that abstinent smokers with the Val/Val genotype performed worse on the n-back test, a test of working memory.16 The reason for these conflicting findings regarding the influence of Val/Val genotype on cognitive performance is not clear. In previous studies, the Val/Val genotype was associated with better or worse performance across many cognitive tasks. It has been argued that while individuals with the Val/Val genotype perform worse on tasks that require cognitive flexibility, they may perform better on tasks that require cognitive stability.54 The N-back is a relatively difficult task that requires sustained attention and working memory function, whereas the mathematical processing task is an easier task that assesses single-digit calculations.54 We did not observe a genotype effect on the Stroop or CPT tasks.

Table 2. Vital and DEQ results as a function of COMT genotype and higher order interactions

| Measure          | COMT | COMT × sex | COMT × race | COMT × dose | Sex | Race |
|------------------|------|------------|-------------|-------------|-----|------|
| Heart rate       | X    | X          | X           | X           |     | X    |
| Systolic BP      | X    | X          | F = 5.27, P = 0.02 | X           |     | X    |
| Diastolic BP     | X    | F = 4.11, P = 0.04 | X           | X           |     | X    |
| Anxious          | F = 4.82, P = 0.03 | Val > Met | X           | X           |     | X    |
| Feel bad         | X    | X          | X           | F = 10.58, P < 0.0001 | X | X |
| Feel down        | X    | X          | X           | F = 7.29, P = 0.0007 | X | X |
| Sedated          | X    | X          | X           | F = 3.43, P = 0.03 | X | X |
| Drug strength    | X    | X          | X           | Val > Met 0.5 NIC F = 7.76, P = 0.0004 | X | X |

Abbreviations: AA, African American; BP, blood pressure; COMT, catechol-O-methyltransferase; DEQ, Drug Effects Questionnaire; EA, European American; F, female; M, male; Met, methionine; NIC, nicotine; Val, valine.

\(\times\) No significant effect (\(P > 0.05\)).

Figure 3. Mean ± s.e.m. of Minnesota Nicotine Withdrawal Scale (MNWS) domains. (a) Difficulty concentrating, (b) irritable as functions of catechol-O-methyltransferase (COMT) genotype and sex.
The underlying mechanisms that mediate the moderating effects of COMT Val158Met on subjective drug effects, withdrawal severity and cognitive performance are an important topic for further research. The high COMT enzyme activity associated with Val allele may reduce tonic DA and increase phasic DA release in subcortical areas as well as reduce DA levels in prefrontal cortical areas.55 This reduced tonic DA release in smokers with the Val allele, may be further accentuated by smoking abstinence, which also reduces DA transmission in subcortical regions.56 As a result, the Val/Val genotype may be associated with more severe withdrawal symptoms. In contrast, the enhanced phasic DA release associated with the Val/Val genotype may contribute to greater responses to some of nicotine’s subjective effects. It is unclear why the COMT Val158Met variation was related to particularly the negative or aversive responses to nicotine. Both the aversive and rewarding effects of nicotine are likely be mediated by DA release in the nucleus accumbens, although the exact mechanisms remain to be determined.

We observed that AA, but not EA, cigarette smokers with the Val/Val genotype had significantly higher systolic and diastolic blood pressure readings throughout the session. In previous studies, the Val/Val genotype has been associated with higher blood pressure in mainly EA populations.57,58 To our knowledge, the influence of the COMT Val158Met polymorphism on blood pressure regulation in cigarette smokers has not been examined. The underlying mechanism for the association of the Val/Val genotype with higher blood pressure in AA smokers is unclear. Previous studies have shown that AAs excrete less sodium and are more salt sensitive than EAs.59–61 DA has an important role in blood pressure regulation, primarily by influencing sodium excretion from the kidneys. Other mechanisms, such as the noradrenergic system, may also contribute to our findings, although the role of COMT Val158Met polymorphism on norepinephrine function has not been well described. Higher systolic and diastolic blood pressure in AA cigarette smokers with the Val/Val genotype may have noteworthy health and treatment implications, especially given the cardiovascular risks associated with smoking.62

Our results also indicated a significant sex-by-COMT interaction for withdrawal severity. Women with the Val/Val genotype reported greater difficulty concentrating and irritability than men who were with Val/Val or Met carriers. These findings are consistent with the sexually dimorphic activity of the COMT enzyme that may be mediated by multiple mechanisms including the estrogen response element in COMT promoter, reduced COMT mRNA expression by estradiol as well as breakdown of catechol estrogens by the COMT enzyme.63 Similar to our findings, other studies have shown that the Val/Val genotype may have greater influence in women for endophenotypes related to negative affect.53,64 The association of greater irritability, and difficulty concentrating with the Val/Val genotype in women may contribute to greater difficulty of women quitting smoking than men. As mentioned before, the Val/Val genotype may be a risk factor for developing nicotine addiction65 and poor treatment response to smoking cessation treatments.11–13 Whether COMT variation contributes to the greater difficulty of women to quit smoking remain to be examined.

Our study also had several limitations. First, because of the small number of smokers with the Met/Met genotype, this group was combined with the Met/Val group. As a result, we could not test for the differences between the Met/Met and Met/Val groups. Similarly, owing to small sample sizes of the race and sex subgroups, we could not conduct detailed analysis to explain race and sex interactions with the COMT Val158Met polymorphism. Second, the smokers were tested once following overnight abstinence from smoking. For optimum assessment of withdrawal or cognitive performance, multiple days of abstinence from smoking may be needed. Third, the IV nicotine responses may not be generalizable to cigarette smoking, given that tobacco addiction includes both nicotinic and non-nicotinic components.65 Fourth, we did not assess smokers during a smoking as usual condition, which would have allowed further delineation of the influence of COMT Val158Met polymorphism on the study outcomes. Finally, we did not correct for multiple testing because of exploratory and hypothesis-generating nature of the study. Thus, the results should be interpreted cautiously, although we fell they warrant replication in larger studies.

Table 3. Subjective and cognitive results as a function of COMT genotype and higher order interactions

| Measure                  | Factor                  | COMT | COMT × sex | COMT × race | COMT × time | Sex | Race |
|--------------------------|-------------------------|------|------------|-------------|-------------|-----|------|
| MNWS                     | Total score             | F = 3.77, P = 0.05 Val > Met | X          | X           | X           | X   | X |
|                          | Crave cigarette         | F = 7.49, P = 0.0072 Val > Met | X          | X           | X           | X   | X |
|                          | Difficulty concentrating| F = 3.89, P = 0.05 Val > Met | F = 3.87, P = 0.05 Val > M Val | X           | X           | X   | X |
|                          | Irritable               | F = 8.41, P = 0.0045 Val > Met | F = 4.46, P = 0.04 Val > M Val | X           | X           | X   | X |
|                          | Factor 1                | F = 4.44, P = 0.04 Val > Met | F = 4.46, P = 0.04 Val > M Val | X           | X           | X   | X |
|                          | Factor 2                | F = 6.12, P = 0.01 Val > Met | F = 4.46, P = 0.04 Val > M Val | X           | X           | X   | X |
| Cognitive                | Math throughput score   | F = 5.03, P = 0.03 Val > Met | X          | X           | X           | X   | X |
|                          | CPT                     | X    | X          | X           | X           |     |     |
|                          | Stroop                  | X    | X          | X           | X           |     |     |

Abbreviations: BQSU, Brief Questionnaire on Smoking Urges; CPT, Continuous Performance Test; COMT, catechol-O-methyltransferase; Met, methionine; MNWS, Minnesota Nicotine Withdrawal Scale; Val, valine.

X No significant effect (P < 0.05).
With these caveats in mind, our results have several treatment implications. As suggested by previous studies, the association of the Val/Val genotype with greater withdrawal severity, worse cognitive performance and greater negative subjective effects suggests that smokers with this genotype, especially female smokers, may experience greater difficulty with smoking cessation. If greater activity of the COMT enzyme is associated with a poor treatment response for smoking cessation, then COMT inhibitors such as tolcapone and entacapone may improve outcomes for smoking cessation in smokers with the Val/Val genotype. Pharmacological COMT inhibition via increased synaptodendritic levels improved working memory function and reduced marijuana craving.66–68 This treatment may be especially helpful for female smokers if it is provided immediately after the quit date when the withdrawal severity is high and smokers are most likely to relapse.

CONFLICT OF INTEREST

MS serves as an expert witness on behalf of Pfizer in lawsuits related to varenicline.

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REFERENCES

1 Sifflstein M, Kolachana B, Simpson EH, Tabares P, Cheng B, Duval M et al. COMT genotype predicts cortical-limbic D1 receptor availability with 11CJNNC112 and PET. Mol Psychiatry 2008; 13: 821–827.
2 Axelrod J, Tomchick R. Enzymatic O-methylation of epinephrine and other catecholamines and other biogenic amines. Pharmacol Rev 1966; 18: 95–113.
3 Lachman HM, Papolos DF, Saito T, Yu YM, Szumlanski CL, Weinsilbom RM. Human catechol-O-methyltransferase pharmacogenetics: description of a functional polymorphism and its potential application to neuropsychiatric disorders. Pharmacogenetics 1996; 6: 243–250.
4 Weinsilbom RM, Otterness DM, Szumlanski CL. Methylation pharmacogenetics: catechol-O-methyltransferase, thioiprin methyltransferase, and histamine N-methyltransferase. Annu Rev Pharmacol Toxicol 1999; 39: 19–52.
5 Egan MF, Goldberg TE, Kolachana BS, Callicott JH, Mazzanti CM, Straub RE et al. Effect of COMT Val108/158 Met genotype on frontal lobe function and risk for schizophrenia. Proc Natl Acad Sci USA 2001; 98: 6917–6922.
6 Opmeer EM, Korteeka R, Alenam A. Depression and the role of genes involved in dopamine metabolism and signalling. Prog Neurobiol 2010; 92: 112–133.
7 Costas J, Sanjuan J, Ramos-Rios R, Perez A, Agra S, Ivorra JL et al. Heterozygosity at catechol-O-methyltransferase Val158Met and schizophrenia: new data and meta-analysis. J Psychiatr Res 2011; 45: 7–14.
8 Tammineni AE, Mannisto PT. Are genetic variants of COMT associated with addiction? Pharmacogenet Genomics 2010; 20: 717–741.
9 Hyman SE, Malenka RC, Nestler EJ. Neural mechanisms of addiction: the role of reward-related learning and memory. Annu Rev Neurosci 2006; 29: 565–598.
10 Colliga S, Lerman C, Shields PG, Jepson C, Krollstalls M, Berlin J et al. Association of catechol-O-methyltransferase with smoking cessation in two independent studies of women. Pharmacogenet Genomics 2005; 15: 393–398.
11 Munao MR, Johnstone EC, Guo B, Murphy MF, Aveyard P. Association of COMT Val108/158 Met genotype with smoking cessation. Pharmacogenet Genomics 2008; 18: 121–128.
12 Omidvar M, Stolk L, Littenrinden AG, Hofman A, Van Duijn CM, Tiemeier H. The effect of catechol-O-methyltransferase Met/Val functional polymorphism on smoking cessation: retrospective and prospective analyses in a cohort study. Pharmacogenet Genomics 2009; 19: 45–51.
13 David SP, Munao MR. Genetic variation in the dopamine pathway and smoking cessation. Pharmacogenomics 2006; 9: 1307–1321.
14 McKinney EF, Walton RT, Yudkin P, Fuller A, Haldar NA, Mant D et al. Association between polymorphisms in dopamine metabolic enzymes and tobacco consumption in smokers. Pharmacogenomics 2000; 10: 483–491.
15 Loughead J, Wileyto EP, Valdez JN, Sanborn P, Tang K, Stasser AA et al. Effect of abstinence challenge on brain function and cognition in smokers differs by COMT genotype. Mol Psychiatry 2009; 14: 820–826.
16 Wang Z, Ray R, Faith M, Tang K, Wileyto EP, Dretz JA et al. Nicotine abstinence-induced cerebral blood flow changes by genotype. Neurosci Lett 2008; 438: 275–280.
17 Egan MF, Hyde TM, Bonoma JB, Mattay VS, Bigelow LB, Goldberg TE et al. Relative risk of neurological signs in siblings of patients with schizophrenia. Am J Psychiatry 2001; 158: 1827–1834.
18 Dreher JC, Kohn P, Kolachana B, Weinberger DR, Berman KF. Variation in dopamine genes influences responsiveness of the human reward system. Proc Natl Acad Sci USA 2009; 106: 617–622.
19 Wichers M, Aguilera M, Kennis G, Krabbendam L, Myin-Germeys I, Jacobs N et al. The catechol-O-methyl transferase Val158Met polymorphism and experience of reward in the flow of daily life. Neuropsychopharmacology 2008; 33: 3030–3036.
20 Htun NC, Miyaki K, Song Y, Ikeda S, Shimbo T, Muramatsu M. Association of the catechol-O-methyl transferase gene Val158Met polymorphism with blood pressure and prevalence of hypertension: interaction with dietary energy intake. Am J Hypertens 2011; 24: 1022–1026.
21 Sofuoglu M, Yoo S, Hill KP, Mooney M. Self-administration of intravenous nicotine in male and female cigarette smokers. Neuropsychopharmacology 2008; 33: 715–720.
22 Sofuoglu M, Herman Al, Nadim H, Jatlow P. Rapid nicotine clearance is associated with greater reward and heart rate increases from intravenous nicotine. Neuropsychopharmacology 2012; 37: 1509–1516.
23 First MB, Spitzer RL, Gibbon M, Williams JBW. Structured Clinical Interview for DSM-IV: Axis I Disorders—Patient Edition (SCID-P, Version 2.0). Biometrics Research Department, New York State Psychiatric Institute: New York, NY, USA, 1995.
24 Sofuoglu M, Mouraditis M, Yoo S, Culligan K, Kosten T. Effects of tiagabine in combination with intravenous nicotine in overnight abstinence smokers. Psychopharmacology (Berl) 2005; 181: 504–510.
25 Sofuoglu M, Poling J, Mouraditis M, Kosten T. Effects of topiramate in combination with intravenous nicotine in overnight abstinence smokers. Psychopharmacology (Berl) 2006; 184: 645–651.
26 Sofuoglu M, Waters AJ, Mooney M, O’Malley SS. Minocycline reduced craving for cigarettes but did not affect smoking or intravenous nicotine responses in humans. Pharmacol Biochem Behav 2009; 92: 135–140.
27 Benowitz NL, Jacob III P, Abijevych KL, Jarvis MJ, Hall S, Lehoheuze JC et al. Biochemical verification of tobacco use and cessation. Nicotine Tob Res 2002; 4: 149–159.
28 al’Absi M, Amurenud T, Wittmers LE. Psychophysiological effects of nicotine abstinence and behavioral challenges in habitual smokers. Pharmacol Biochem Behav 2002; 72: 707–716.
29 Mendelson JH, Sholar MB, Goletiani N, Siegel AJ, Mello NK. Effects of low- and high-nicotine cigarette smoking on mood states and the HPA axis in men. Neuropsychopharmacology 2005; 30: 1751–1763.
30 Newhouse PA, Sunderland T, Narang PK, Mellow AM, Fertig JB, Lawlor BA et al. Neuroendocrine, physiologic, and behavioral responses following intravenous nicotine in nonsmoking healthy volunteers and in patients with Alzheimer’s disease. Psychoneuroendocrinology 1990; 15: 471–484.
31 Pickworth WB, Fant RV. Endocrine effects of nicotine administration, tobacco and other drug withdrawal in humans. Psychoneuroendocrinology 1998; 23: 131–141.
32 Alexander N, Osinsky R, Mueller E, Schmitz A, Guenthert S, Kueper Y et al. Genetic variants within the dopaminergic system interact to modulate endocrine stress reactivity and recovery. Behav Brain Res 2011; 216: 53–58.
33 Wolff K, Tsapakis EM, Pariante CM, Kerwin RW, Forsling ML, Aitchison KJ. Pharmacogenetic studies of change in cortisol on ecstasy (MDMA) consumption. Journal of psychopharmacology (Oxford, England) 2012; 26: 419–428.
34 Tiffany ST, Dobres DJ. The development and initial validation of a questionnaire on smoking urges. Br J Addict 1991; 86: 1467–1476.
35 Cox LS, Tiffany ST, Christen AG. Evaluation of the brief questionnaire of smoking urges. Behav Res Methods Instrum Comput 2001; 3: 7–16.
36 Bell SL, Taylor RC, Singleton EG, Henningfield JE, Heishman SJ. Smoking after nicotine deprivation enhances cognitive performance and decreases tobacco craving in drug abusers. Nicotine Tobacco Res 1999; 1: 45–52.
37 Morgan MJ, Davies GM, Willner P. The questionnaire of smoking urges is sensitive to abstinence and exposure to smoking-related cues. Behav Pharmacol 1999; 10: 619–626.
38 Hughes JR, Hatsuakmi D. Signs and symptoms of tobacco withdrawal. Arch Gen Psychiatriy 1986; 43: 289–294.
39 Hughes JR, Hatsuakmi DK. Effects of three doses of transdermal nicotine on post-cessation eating, hunger and weight. J Subst Abuse 1997; 9: 151–159.
40 Watson D, Clark LA, Tellegen A. Development and validation of brief measures of positive and negative affect: the PANAS scales. J Pers Soc Psychol 1988; 54: 1063–1070.
42 Reeves D, Kane R, Winter K. Automated Neuropsychological Assessment Metrics (ANAM v2.11a/96) User’s Manual: Clinical and Neurotoxicology Subset. National Cognitive Foundation: San Deigo, CA, USA, 1996, NCFR-SR 96–01.
43 Snyder FR, Henningfield JE. Effects of nicotine administration following 12 h of tobacco deprivation: assessment on computerized performance tasks. Psychopharmacology (Berl) 1989; 97: 17–22.
44 Mancuso G, Warburton DM, Melen M, Sherwood N, Tirelli E. Selective effects of nicotine on attentional processes. Psychopharmacology (Berl) 1999; 146: 199–204.
45 Mancuso G, Andres P, Anseau M, Tirelli E. Effects of nicotine administered via a transdermal delivery system on vigilance: a repeated measure study. Psychopharmacology (Berl) 1999; 142: 18–23.
46 Spreen O, Strauss E. A Compendium of Neuropsychological Tests. Oxford University Press: New York, NY, USA, 1991.
47 Sofuoglu M, Herman AI, Nadim H, Jatlow P. Rapid nicotine clearance is associated with greater reward and heart rate increases from intravenous nicotine. Neuropsychopharmacology 2012; 37: 1509–1516.
48 Dempsey D, Tutka P, Jacob 3rd P, Allen F, Schoedel K, Tyndale RF et al. Nicotine metabolite ratio as an index of cytochrome P450 2A6 metabolic activity. Clin Pharmacol Ther 2004; 76: 64–72.
49 Guo S, Chen da F, Zhou DF, Sun HQ, Wu GY, Haile CN et al. Association of functional catechol O-methyl transferase (COMT) Val158Met polymorphism with smoking severity and age of smoking initiation in Chinese male smokers. Psychopharmacology (Berl) 2000; 155: 945–959.
50 Benowitz NL, Hukkanen J, Jacob 3rd P. Nicotine chemistry, metabolism, kinetics and biomarkers. Handb Exp Pharmacol 2009; 192: 29–60.
51 Pritchard JK, Stephens M, Donnelly P. Inference of population structure using multilocus genotype data. Genetics 2000; 155: 945–959.
52 Yang BZ, Zhao H, Kranzler HR, Gelernter J. Characterization of a likelihood based method and effects of markers informativeness in evaluation of admixture and population group assignment. BMC Genet 2005; 6: 50.
53 Domschke K, Baune BT, Haviik L, Stuhrmann A, Suslow T, Kugel H et al. Catechol-O-methyltransferase gene variant: impact on amygdala response to aversive stimuli. Neuroimage 2012; 60: 2222–2229.
54 Witte AV, Floel A. Effects of COMT polymorphisms on brain function and behavior in health and disease. Brain Res Bull 2012; 88: 418–428.
55 Bilder RM, Volavka J, Lachman HM, Grace AA. The catechol-O-methyltransferase polymorphism: relations to the tonic-phasic dopamine hypothesis and neuropsychiatric phenotypes. Neuropsychopharmacology 2004; 29: 1943–1961.
56 Zhang L, Dong Y, Doyon WM, Dani JA. Withdrawal from chronic nicotine exposure alters dopamine signaling dynamics in the nucleus accumbens. Biol Psychiatry 2012; 71: 184–191.
57 Stewart SH, Orozzi G, Randall PK, Anton RF. COMT genotype influences the effect of alcohol on blood pressure: results from the COMBINE study. Am J Hypertens 2009; 22: 87–91.
58 Hagen K, Pettersen E, Stovner LJ, Skoopen F, Holmen J, Zwart JA. High systolic blood pressure is associated with Val/Val genotype in the catechol-o-methyltransferase gene. The Nord-Trondelag Health Study (HUNT). Am J Hypertens 2007; 20: 21–26.
59 Grim CE, Luft FC, Miller JZ, Meneely GR, Battarbee HD, Hames CG et al. Racial differences in blood pressure in Evans County, Georgia: relationship to sodium and potassium intake and plasma renin activity. J Chronic Dis 1980; 33: 87–94.
60 Chrysant SG, Danisa K, Kern DC, Dillard BL, Smith WJ, Frohlich ED. Racial differences in pressure, volume and renin interrelationships in essential hypertension. Hypertension 1979; 1: 136–141.
61 Luft FC, Grim CE, Higgins Jr. JT, Weinberger MH. Differences in response to sodium administration in normotensive white and black subjects. J Lab Clin Med 1977; 90: 555–562.
62 Armani C, Landini Jr. L, Leone A. Molecular and biochemical changes of the cardiovascular system due to smoking exposure. Curr Pharm Des 2009; 15: 1038–1053.
63 Tunbridge EM, Harrison PJ. Importance of the COMT gene for sex differences in brain function and predisposition to psychiatric disorders. Curr Topics Behav Neurosci 2011; 8: 119–140.
64 Olsson CA, Arney RJ, Loft-Miri M, Byrnes GB, Williamson R, Patton GC. Association between the COMT Val158Met polymorphism and propensity to anxiety in an Australian population-based longitudinal study of adolescent health. Psychiatr Genet 2005; 15: 109–115.
65 Sofuoglu M, Lesage MG. The reinforcement threshold for nicotine as a target for tobacco control. Drug Alcohol Depend 2012; 125: 1–7.
66 Apud JA, Matray V, Chen J, Kolachana BS, Callicott JH, Rasetti R et al. Tolcapone improves cognition and cortical information processing in normal human subjects. Neuropsychopharmacology 2007; 32: 1011–1020.
67 Roussos P, Giakoumaki SG, Bitsios P. Tolcapone effects on gating, working memory, and mood interact with the synonymous catechol-O-methyltransferase rs4818c/g polymorphism. Biol Psychiatry 2009; 66: 997–1004.
68 Shafa R. COMT- inhibitors may be a promising tool in treatment of marijuana addiction trials. A J Addict 2009; 18: 322.