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Dopamine D4 Receptor Gene Variation Moderates the Efficacy of Bupropion for Smoking Cessation

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Abstract

Smokers (≥10 cig/day; *N* =331) of European ancestry taking part in a double-blind placebo-controlled randomized trial of 12 weeks of treatment with bupropion plus counseling for smoking cessation were genotyped for a VNTR polymorphism in Exon-III of the Dopamine D4 receptor (*DRD4*) gene. Generalized estimating equations predicting point-prevalence abstinence at end of treatment and 2, 6, and 12-months post-end of treatment indicated that bupropion (vs. placebo)

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Conflict of Interest

The authors declare no conflict of interest.

predicted increased odds of abstinence. The main effect of Genotype was not significant. A Genotype × Treatment interaction (p=.005) showed that bupropion predicted increased odds of abstinence in long-allele carriers (OR=1.31, p<.0001), whereas bupropion was not associated with abstinence among short-allele homozygotes (OR=1.06, p=.23). The Genotype × Treatment interaction remained when controlling for demographic and clinical covariates (p=.01) and in analyses predicting continuous abstinence (ps≤.054). Bupropion may be more efficacious for smokers who carry the long-allele, which is relevant to personalized pharmacogenetic treatment approaches.

Keywords

DRD4; VNTR; smoking cessation; bupropion; pharmacogenetic

Introduction

Identifying genetic factors that predict smoking cessation outcomes and response to smoking cessation treatments may be important in advancing the state of the science because of the low efficacy of current pharmacotherapies. Furthermore, such data may inform the development of personalized treatment approaches to tobacco addiction and elucidate the underlying mechanisms of nicotine dependence.

A variable number of tandem repeats (VNTR) polymorphism in Exon-III of the Dopamine D4 receptor (*DRD4*) gene (11p15.5) that is putatively functional has been shown to play a role in phenotypes relevant to addiction.[1] Although there are alternate classification schemes for this polymorphism,[2] alleles have been grouped into “long” (L; 7 or more repeats) or “short” (S; 6 or fewer) most consistently in the literature.[3-6] Compared with the S-allele, the L-allele of this polymorphism has been associated with reduced ligand binding,[7] decreased gene expression *in vitro*, and attenuation of cyclic AMP formation when dopamine is bound to the receptor.[8-10] Thus, L-allele carriers may demonstrate low overall dopaminergic tone in areas of the mesolimbic pathway where D4 receptors appear to be distributed,[11-12] although the exact localization of D4 receptors in the human brain is still under investigation.[13-14]

Prior research suggests that the L-allele of the *DRD4* Exon-III VNTR is associated with personality traits that may transmit risk for addiction,[15-16] response to medications for alcohol abuse,[17-18] and enhanced reactivity to substance-related cues,[19-20] including smoking-related stimuli among cigarette smokers.[5, 18, 21] Furthermore, L-allele carriers may have lower tobacco use quit rates and poorer smoking cessation outcomes in some populations.[22-23] Additionally, a recent study of smokers of European ancestry participating in a placebo controlled trial of transdermal nicotine replacement demonstrated that possession of at least one copy of the L-allele was associated with lower abstinence rates at 12-week follow up, but this effect was not observed at the 26-week follow up.[3] Nicotine patch was associated with higher abstinence rates than placebo in that study; however, *DRD4* genotype did not moderate treatment effects. It is possible that medications which

directly target the dopaminergic system may perhaps be more likely to show differential efficacy by *DRD4* genotype.

Sustained-release bupropion is a first-line treatment for smoking cessation, which inhibits dopamine and norepinephrine reuptake and has partial nicotinic receptor agonist properties.[24,25] Previous reports indicate that variation in the dopamine D2 receptor gene region influences the efficacy of bupropion for smoking cessation.[26,27] Conversely, a study of 1295 single nucleotide polymorphisms (SNPs) in 58 genes found that none of the 11 SNPs in *DRD4* that were analyzed moderated the effects of bupropion on smoking cessation outcomes.[28] Similarly, a genome-wide SNP association analysis of pooled samples, including the present study's sample, found no evidence that SNPs within DRD4 influenced bupropion response.[29]

To the best of our knowledge, we are unaware of any published study that has examined whether copy number repeat variants within *DRD4*, such as the Exon-III VNTR, moderate the efficacy of bupropion for smoking cessation. Accordingly, we conducted the present pharmacogenetic analysis to investigate whether the *DRD4* Exon-III VNTR polymorphism moderates the effects of bupropion (vs. placebo) on smoking cessation outcomes.

Materials and Methods

Participants

Participants were 524 individuals recruited via advertisements to take part in a 2 × 2 smoking cessation trial comparing bupropion versus placebo crossed with standard smoking cessation counseling (ST) versus enhanced counseling incorporating cognitive behavioral therapy (CBT) for depression.[30] Exclusion criteria included pregnancy; a history of mood or thought disorder, based on the Diagnostic and Statistical Manual of Mental Disorders, 4th edition;[31] seizure disorder; current use of psychotropic medications; history of seizures or eating disorders; previous use of l-dopa or monoamine oxidase inhibitors; age less than 18 years; or score less than 5 on a 10-point Likert scale of willingness to quit; and smoking less than 10 cigarettes per day. The final sample for analysis included only those who consented for genotyping and reported being of white European descent to reduce potential bias due to racial admixture (N = 331). Subjects contributing DNA had significantly higher proportions of females, were older, and had been smoking longer.

Procedure

Following screening and intake procedures, which have been detailed previously,[30] participants were randomized in double-blind fashion to bupropion or placebo, according to gender, current depressive symptoms, and levels of nicotine dependence, using the urn randomization technique. Bupropion treatment was delivered according to the standard therapeutic dose (150 mg/day for the first 3 days, followed by 300 mg/day) for a total of 12 weeks. Medication was delivered concurrently along with the two randomly-assigned counseling conditions (ST vs. CBT), both of which involved 12 two-hour sessions (see Brown et al.[30] for more details about the counseling interventions). Counseling condition did not moderate genotype or medication effects, thus it was not retained in the analysis.

Measures

Genotyping—Blood samples were separated and frozen on the day of receipt. Plasma and buffy coat lymphocytes were stored at 80°C at the Miriam Hospital (Providence, RI, USA) and the Primary Care Genetics Laboratory & Translational Research Center at Memorial Hospital of Rhode Island (Pawtucket, RI, USA) until required for analysis. DNA was extracted using standard techniques described elsewhere.[32] DNA was genotyped at the National Institute on Drug Abuse Molecular Neurobiology Laboratory (Baltimore, MD, USA) using methods previously described and briefly summarized here. The *DRD4* VNTR was amplified by polymerase chain reaction (PCR) using primers and methods previously described.[10], [33] After separation by electrophoresis for 3 h on a 2.5% agarose gel, the PCR products (2–8- or 10-repeat units) were sized using a 50 bp ladder.

This polymorphism involves a 48 basepair sequence that is repeated between 2 and 11 times with the most common versions being 2, 4, and 7 repeats. *DRD4* VNTR alleles were classified as long (L) if they consisted of seven or more repeats, and short (S) if they consisted of six or fewer repeats, and participants were grouped into those with at least one copy L-allele (SL + LL genotypes) versus those with no copies (SS genotypes), consistent with previous studies.[1], [3] Genotype frequencies were not significantly different across treatment conditions and did not deviate from Hardy-Weinberg proportions. Genotype frequencies by treatment condition are reported in the top of Table 1.

Baseline characteristics—Gender, education, marital status, age, ethnic ancestry, and smoking history variables (cig/day, age started smoking, years smoking, number of serious quit attempts were assessed by self-report during the pretreatment assessment visit. Depressive symptoms were measured on the same visit using the Center for Epidemiologic Studies Depression Scale (CESD),[34] a well-validated tool for assessing depressive symptom severity among non-psychiatric populations. Baseline nicotine dependence severity was assessed using the Fagerström Test of Nicotine Dependence (FTND),[35] a widely used and well-validated measure.

Smoking outcomes—Consistent with prior reports,[3], [26]-[27] 7-day point prevalence abstinence (i.e., seven continuous days without any smoking), verified biochemically on the basis of cotinine levels (≥ 15 ng/ml classified as abstinent) at end of treatment (EOT) and at 2-, 6-, and 12-months post end of treatment, was the primary outcome. This approach does not account for brief lapses back to smoking following quit day and treats participants who undergo lapses and then reinitiate and maintain abstinence in between outcome assessments as successful abstainers. Participants lost to follow-up were classified as smokers for all outcome analyses, consistent with prior investigations and established practice.[26], [36] Continuous abstinence at EOT, 6-, and 12-months follow up was analyzed as a secondary outcome.

Analyses

Preliminary analyses involved Chi-square tests (for categorical variables) and ANOVAs (for continuous variables), which compared baseline characteristics listed in Table 1 across treatment conditions and across genotype within each treatment condition. Consistent with

published recommendations,[37] the primary analysis involved generalized estimating equations (GEE) with unstructured covariance matrices specified. Baseline GEE models including Genotype (SL+LL vs. SS), Treatment (Bupropion vs. Placebo), and Time (EOT, 2, 6, and 12 mo follow up) as predictors and 7-day point prevalence abstinence (abstinent vs. non-abstinent) as the outcome were first tested. Full GEE models, which added the Genotype × Treatment interaction to the baseline models were then performed. Additional GEE models demonstrated that Genotype × Time and Genotype × Treatment × Time interactions were non-significant and therefore dropped. Significant Genotype × Treatment interactions were followed up with simple effect models, which tested the treatment effect separately across subsamples stratified by Genotype. Results of GEE models are reported as Odds Ratios (*OR*s) with 95% Confidence intervals (*CI*s). All models were tested both unadjusted and adjusted for all demographic and clinical characteristics listed in Table 1.

For continuous abstinence outcomes, Genotype, Treatment, and the Genotype × Treatment interaction were predictors in separate logistic regression models for each outcome time point in unadjusted models and models adjusting for baseline demographic and clinical characteristics.

For descriptive purposes, logistic regression models predicting abstinence rates by treatment condition for each follow up point within each genotype group were performed and *OR*s (95% *CI*s) are reported. Alpha level was set to .05 for all analyses.

Results

Baseline Characteristics

Baseline characteristics by genotype and treatment group are presented in Table 1. There were no significant differences in demographics, smoking characteristics, or depressive symptoms across treatment condition nor were there any differences across genotype within each treatment group.

Seven-Day Point Prevalence Outcomes

Results of GEE models predicting 7-day point prevalence outcomes are reported in Table 2. In comparison to placebo, bupropion was associated with increased odds of abstinence in both the unadjusted and adjusted baseline models. The main effect of Genotype in the overall sample was not significant.

There was a significant Genotype × Treatment interaction in both the unadjusted and adjusted full GEE models (Figure 1 and Table 2). As illustrated in Table 2, simple effect GEE analyses indicated that bupropion (vs. placebo) was associated with increased odds of abstinence in SL+LL participants (n = 102), but did not have a significant effect in SS participants (n = 229). This overall pattern of results remained consistent when adjusting for demographics, smoking characteristics, and depressive symptoms. In all GEE analyses, there was a significant main effect of time indicating that abstinence rates were higher at earlier outcome assessments.

Abstinence rates by genotype and treatment are reported in Figure 1. Among SL+LL participants, logistic regression models predicting 7-day point prevalence abstinence at each assessment point indicated significantly higher abstinence rates in the bupropion compared to the placebo condition at EOT [*OR* (95% *CI*) = 5.70 (2.39 – 13.62), $p < .0001$], 2 month [*OR* (95% *CI*) = 5.50 (2.14 – 14.16), $p = .0004$], and 6 month [*OR* (95% *CI*) = 10.36 (2.80 – 38.31), $p = .0005$] follow ups, and a non-significant trend favoring bupropion at the 12 month follow up [*OR* (95% *CI*) = 2.83 (0.89 – 9.00), $p = .08$]. In SS participants, treatment differences were significant only at EOT [*OR* (95% *CI*) = 1.79 (1.06 – 3.02), $p = .03$], and non-significant at 2 month [*OR* (95% *CI*) = 1.58 (0.92 – 2.73), $p = .10$], 6 month [*OR* (95% *CI*) = 1.12 (0.61 – 2.05), $p = .72$], and 12 month [*OR* (95% *CI*) = .92 (0.48 – 1.74), $p = .79$] follow ups.

Based on inspection of abstinence rates, additional unplanned simple effect GEE analyses predicting point prevalence abstinence from genotype within each treatment group were calculated. In those randomized to placebo ($n = 169$), SS+SL (vs. LL) was significantly associated with reduced odds of abstinence in unadjusted, *OR* (95% *CI*) = 0.85 (0.77 - 0.93), $p = .0006$, and adjusted, *OR* (95% *CI*) = 0.88 (0.80 - 0.97), $p = .0009$, models. In those randomized to bupropion ($n = 162$), genotype was not associated with abstinence in unadjusted, *OR* (95% *CI*) = 1.06 (0.93 - 1.19), $p = .38$, or adjusted, *OR* (95% *CI*) = 1.06 (0.93 - 1.21), $p = .39$, models.

Continuous Abstinence Outcomes

Logistic regression models predicting continuous abstinence showed near-significant or significant Genotype × Treatment interactions at EOT (Wald $\chi^2 = 3.7$, $p = .054$), 6 month (Wald $\chi^2 = 9.8$, $p = .002$), and 12 month (Wald $\chi^2 = 4.2$, $p = .04$) follow ups. Adjusting for baseline demographic and clinical characteristics did not substantially alter the effects of Genotype × Treatment interactions (EOT: Wald $\chi^2 = 3.5$, $p = .06$; 6 months: Wald $\chi^2 = 8.7$, $p = .003$; 12 months: Wald $\chi^2 = 3.6$, $p = .06$). Continuous abstinence rates in the SL+LL group, by treatment (bupropion vs. placebo), were as follows: EOT [41% vs. 11%, *OR* (95% *CI*) = 5.86 (2.09 – 16.43), $p = .0008$], 6 month [35% vs. 4%, *OR* (95% *CI*) = 14.40 (3.10 – 66.90), $p = .0007$], and 12 month [17% vs. 4%, *OR* (95% *CI*) = 5.68 (1.14 – 28.27), $p = .03$] follow-up. Continuous abstinence rates in the SS group, by treatment, were: EOT [35% vs. 23%, *OR* (95% *CI*) = 1.83 (1.02 – 3.27), $p = .04$], 6 month [22% vs. 21%, *OR* (95% *CI*) = 1.02 (0.54 – 1.92), $p = .95$], and 12 month [14% vs. 15%, *OR* (95% *CI*) = 0.90 (0.43 – 1.89), $p = .79$].

Discussion

The *DRD4* Exon-III VNTR polymorphism moderated the effects of bupropion (vs. placebo) on smoking cessation outcomes in this study. Participants with at least one copy of the L-allele had increased abstinence rates following bupropion (vs. placebo) treatment, whereas bupropion evidenced minimal efficacy beyond placebo among smokers with SS genotypes. Additional simple effect analyses also showed that L-allele carriers treated with placebo exhibited a higher risk of relapse than participants with the SS genotype, and this risk was offset by bupropion treatment. This pattern of findings was generally consistent across

multiple outcomes (i.e., point prevalence and continuous abstinence) and in adjusted models that accounted for the effects of demographic and clinical characteristics.

The present results are concordant with prior pharmacogenetic analyses demonstrating that polymorphisms related to dopaminergic activity are associated with smoking cessation outcomes and that such variants may moderate the efficacy of bupropion.[26–27, 38] Furthermore, they add to an emerging literature indicating the *DRD4* Exon-III VNTR polymorphism is associated with addiction-related phenotypes, including smoking cessation.[1, 3, 22–23]

To the best of our knowledge this is the first published pharmacogenetic investigation of the *DRD4* Exon-III VNTR and bupropion treatment for smoking cessation. In a previous pharmacogenetic study of this gene and nicotine patch (vs. placebo) treatment, carriers of the L-allele exhibited greater relapse risk at the 12-week follow up,[3] which parallels the pattern of results in the placebo arm of the current study. By contrast, the Exon-III VNTR polymorphism did not predict outcome at 26 weeks follow up in that study, nor did it interact with nicotine replacement therapy to predict outcome. Furthermore, the C→T position 521 SNP in *DRD4* also did not predict outcomes in that study. Similarly, multi-gene and genome-wide SNP association studies using more stringent type-I error corrections found that SNPs within *DRD4* do not have a significant main effect on nor significantly interact with bupropion treatment to predict smoking cessation outcomes.[28–29]

The L-allele of this VNTR polymorphism may produce structural changes to the length of the protein in the D4 receptor's third cytoplasmic loop, which is associated with reduced receptor binding affinity and diminished signaling in response to dopamine binding.[7–10] There is also suggestive evidence that the L-allele is associated with reduced gene expression in human brain tissue,[42] potentially via its effect on RNA stability or translational efficiency.[43] Given the potential functional effects of the *DRD4* Exon-III VNTR, one may speculate why this polymorphism moderated efficacy of bupropion in the current study, but did not moderate the efficacy of nicotine replacement therapy in David et al.[3] One explanation is that the L-allele results in low dopaminergic tone, which may in turn increase relapse risk, and bupropion is better able to ameliorate this deficit than nicotine replacement therapy because it acts more directly on the dopaminergic system. Although this explanation would be consistent with recent findings indicating that variants in the Catechol-O-Methyltransferase gene that may result in low dopaminergic tone are associated with better bupropion response,[38] it is unclear how to integrate these findings with other evidence indicating that polymorphisms linked with low D2 receptor availability may be associated with poorer bupropion response.[26–27] Based on the current finding and the results of David et al.,[3] one hypothesis is that, in the context of smoking cessation treatment, L-allele carriers of European decent may perhaps benefit more from bupropion as opposed to nicotine replacement therapy. However, because the two studies sampled from distinct populations and had other methodological differences, a direct comparison of smokers prospectively genotyped for *DRD4* and then experimentally randomized either to bupropion or nicotine replacement therapy by genotype is required to systematically evaluate this prediction.

A genotype × treatment interaction and an association between the L-allele and abstinence outcomes within the placebo arm were found in this study. Accordingly, one might expect that, provided there is sufficient sample size, a main effect of genotype could also be apparent when averaged across treatment groups, albeit this effect would be weakened by the lack of genotype effect in the bupropion condition. However, the main effect of genotype in the overall sample was not statistically significant [Unadjusted GEE model: *OR* (95% *CI*) = 0.94 (0.87 -1.02), $p = .13$]. One possible explanation for the lack of the significant main effect of genotype is that our sample was not large enough to detect such an effect. Indeed, David et al.'s placebo-controlled nicotine replacement pharmacogenetic analysis required a sample that was twice as large as the current sample ($N = 720$) to demonstrate a main effect of the *DRD4* Exon-III VNTR on 12-week cessation outcomes ($p = .034$).[3]

The genotype × treatment interaction did not significantly vary by time. Follow up analyses among L-allele carriers suggested relatively robust bupropion vs. placebo effects that endured through the 6-month follow up, and were weakened at the 12-month follow up (*OR*s ranging 2.83 – 10.36 across all assessments). By contrast, treatment effects for participants with the SS genotype were comparatively weaker across all assessments and eroded to non-significance after the EOT assessment (*OR*s ≤ 1.52 across all assessments). Similar patterns of abstinence rates by treatment and genotype over time have been demonstrated in a prior analysis of the *DRD2* Taq1A polymorphism and bupropion for smoking cessation.[27] Extant research suggests that the L-allele is associated with greater craving,[39] attentional capture,[5] and brain activation[21] in response to smoking-related stimuli, suggesting that incentive sensitization processes triggered by smoking-paired cues may potentially contribute to relapse among L-allele carriers. There is some evidence to suggest that bupropion[40] (but not nicotine patch)[41] diminishes cue-induced craving, which could help to extinguish the condition craving response and possibly render smoking-associated stimuli less potent following active treatment. Speculatively, bupropion may buffer L-allele carriers from the relapse-producing effects of cue exposure even after active treatment is terminated, which could account for the persistent treatment effects in smokers with the L-allele. However, further research is required to determine whether this putative mechanism accounts the pharmacogenetic effects of *DRD4* on bupropion efficacy.

Some limitations should be noted. A small portion of participants did not contribute DNA. These individuals were different from members of the primary sample on some baseline variables, which may have altered the generalizability of the present sample. We only included participants who reported being from white European descent in analyses to reduce potential bias due to racial admixture. Genotyping ancestry informative markers would have been preferable, given the limitations of self-report. Additionally, we did not have a large enough sample of non-Europeans for multi-subgroup analyses, leaving unclear whether these findings will extend across other ancestral groups. It should be noted that three other genes have been analyzed in this sample.[26,27] Thus, a more conservative approach would have been to adjust the alpha level for multiple tests. Given the small sample, we retained the standard alpha level of .05 to increase power to detect potential effects. Even if we adopted a more stringent significance level of .0125 (.05 / 4 total genes tested in this

sample), most of the primary findings would have retained significance, with the exception of the Gene × Treatment interaction in the adjusted model that yielded a *p*-value of .014. Finally, as mentioned above, this sample may have been too small to provide sufficient power to detect a main effect of genotype in the overall sample.

In sum, this investigation suggests that individuals who carry the L-allele of the Exon-III *DRD4* VNTR polymorphism exhibit a better clinical response to bupropion (vs. placebo) for smoking cessation than non-carriers. If replicated and extended, these findings may eventually lead to clinical applications of genetically tailored smoking cessation therapy using bupropion with the *DRD4* gene.

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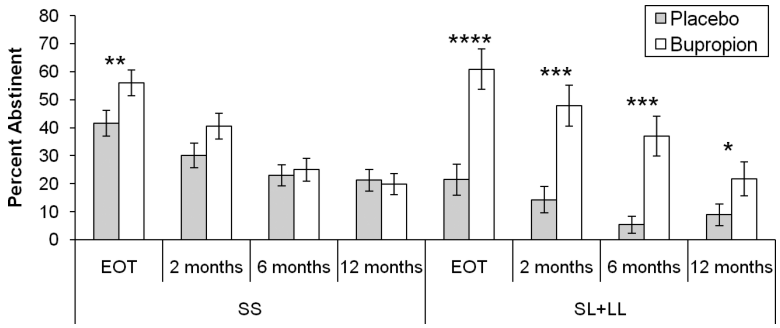

[1]Seven-day point prevalence abstinence percentages (± *SE*) by treatment and genotype. SS = Homozygous for short allele; SL+LL ≥ 1 copy of long allele. Placebo vs. Bupropion comparisons: **p* < .10, ***p* < .05 ****p* < .0005, *****p* < .0001

Table 1

Baseline Characteristics of Sample, by Genotype and Treatment

		Placebo		Bupropion	
	Entire sample (*N* = 331)	**SS (*n* = 113)**	**SL+LL (*n* = 56)**	**SS (*n* = 116)**	**SL+LL (*n* = 46)**
Demographics					
Age, *M*(*SD*)	45.86 (10.72)	46.5 (10.6)	44.7 (11.6)	45.6 (10.7)	46.4 (10.4)
Female, *n* (%)	164 (49.5)	51 (45.1)	32 (57.1)	54 (46.6)	27 (58.7)
Married, *n* (%)	210 (63.4)	75 (66.4)	32 (57.1)	79 (68.1)	25 (54.3)
Employed, *n* (%)[a]	252 (78.0)	90 (83.3)	39 (73.6)	85 (75.2)	38 (82.6)
Completed high school, *n* (%)	306 (92.4)	107 (94.7)	49 (87.5)	109 (94.0)	41 (89.1)
Baseline Characteristics, *M*(*SD*)[b]					
FTND score	6.18 (1.79)	5.95 (1.77)	6.56 (1.90)	6.27 (1.76)	6.02 (1.64)
Cig/day	23.36 (8.63)	23.58 (9.08)	24.21 (9.07)	23.16 (8.27)	22.20 (7.98)
Age started smoking	17.20 (4.49)	17.64 (4.13)	16.59 (2.55)	16.90 (5.36)	17.58 (5.00)
Years smoking	26.93 (11.11)	27.30 (11.37)	27.41 (11.84)	26.54 (10.55)	26.38 (11.17)
No. of serious quit attempts	3.33 (2.31)	3.36 (2.45)	3.29 (2.01)	3.27 (2.28)	3.45 (2.46)
CESD score	6.41 (6.72)	5.85 (6.42)	6.76 (7.20)	6.09 (6.27)	8.18 (7.76)

Note. SS = Homozygous for short allele; SL+LL ≥ 1 copy of long allele; FTND = Fagerström Test of Nicotine Dependence; CESD = Center for Epidemiologic Studies Depression Scale.

[a] *N* = 323 because of missing data

[b] *N*s range from 286 to 331 because of missing data on these measures.

Table 2

Results of Generalized Estimating Equation Analyses of Point Prevalence Abstinence

	Unadjusted		Adjusted[a]	
	***OR* (95% *CI*)**	***p***	***OR* (95% *CI*)**	***p***
Baseline Model				
Time	0.91 (0.89 – 0.93)	<.0001	0.91 (0.89 – 0.92)	<.0001
Genotype	0.94 (0.87 - 1.02)	.13	0.95 (0.87 – 1.03)	.28
Treatment	1.13 (1.05 – 1.22)	.001	1.16 (1.07 – 1.26)	.0004
Full Model				
Genotype × Treatment	1.25 (1.07 – 1.46)	.005	1.24 (1.05 – 1.46)	.014
Simple Effect in SS (*n* = 229)				
Treatment	1.06 (0.96 – 1.16)	.23	1.09 (0.99 – 1.21)	.08
Time	0.91 (0.89 – 0.93)	<.0001	0.90 (0.88 – 0.93)	<.0001
Simple Effect in SL+LL (*n* = 102)				
Treatment	1.32 (1.16 – 1.49)	<.0001	1.34 (1.17 – 1.54)	<.0001
Time	0.92 (0.89 – 0.95)	<.0001	0.91 (0.87 -0.95)	<.0001

Note. Bupropion: SS (*n* = 116), SL+LL (*n* = 46); Placebo: SS (*n* = 113), SL+LL (*n* = 56); Variable Coding: Abstinence (abstinent vs. non-abstinent), Genotype (SL+LL vs. SS), Treatment Bupropion vs. Placebo.

[a]Adjusted for age, sex, employment, education, FTND, CESD, age started smoking, yrs. smoking, no. of prior quit attempts, cig/day; SS = Homozygous for short allele; SL+LL ≥ 1 copy of long allele; FTND = Fagerström Test of Nicotine Dependence; CESD = Center for Epidemiologic Studies Depression Scale.