Electronic Supplementary Material:

Title: Benefits of varenicline vs. bupropion for smoking cessation: A Bayesian Analysis of the Interaction of Reward Sensitivity and Treatment

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SUPPLEMENTARY METHODS FOR PICTURE VIEWING AND ERP ANALYSIS

Picture-Viewing Task

During the 30-min picture viewing task, participants viewed one of three picture sets composed of four picture categories: pleasant (PLE), unpleasant (UNP), cigarette-related (CIG), and neutral (NEU). Each category included 24 pictures (96 total pictures per set). The pictures were selected from the International Affective Picture System (IAPS) pictures (Lang et al. 2005) and from other sets developed by us (Carter et al. 2006, Versace et al. 2011) and others (Gilbert and Rabinovich 1999, Stritzke et al. 2004). The pictures consisted of both high and low arousal contents: erotic and romantic couples, food and landscapes (PLE); mutilations, grief, disease (UNP); people, household objects (NEU); people smoking, cigarette-related objects (CIG).

Pictures in the PLE category (natural rewards) were comprised of erotic couples (high arousal), romantic couples (low arousal), and pleasant objects (e.g. food, landscapes (low arousal)); the UNP category consisted of mutilations (high arousal), sad scenes (e.g., grief, disease; low arousal), and unpleasant objects (e.g., pollution, accidents; low arousal); the NEU category involved pictures of neutral people and neutral objects (e.g., household objects), and the CIG category contained pictures of people smoking and cigarette-related objects (e.g., lit cigarettes in ashtrays). Pictures were presented for 4 s, separated by a random inter-trial interval of 3-5 s, in pseudo-random sequences with no more than two pictures of the same category presented consecutively. Each picture was presented twice during the session to increase the ERP signal-to-noise ratio. Further details of the pictures are provided in previous reports (Robinson et al. 2013).

ERP Data Collection Analyses and LPP Response Categorization

Details of the EEG collection, offline scoring, analyses, and derivation of the reward sensitivity categories are reported previously (Versace et al. 2012). Briefly, we collected EEG during the picture viewing task using a 129-channel EEG net referenced to the Cz electrode site. Offline scoring included filtering (Junghöfer et al. 2000), eye blink correction (Ille et al. 2002), segmentation using a 900 ms window with a 100 ms baseline preceding the picture, and calculation of the mean LPP amplitude between 400 and 700 ms after picture onset for each category (UNP, NEU, PLE, CIG) for each participant by averaging over ten sensors in the central and parietal regions.

As noted in our original report (Versace et al. 2012), the LPP values for the 4 picture categories were entered into a *k*-means cluster analysis in which 99 (55%) were assigned to Cluster 1 and 81 (45%) to Cluster 2. The significant cluster by valence interaction ($F_{(3,534)}$=43.49; p<.0001), described in our original report, indicated that although both NEU and UNP pictures prompted similar brain responses in the two groups, CIG pictures prompted a significantly larger LPP than PLE pictures in Cluster 2 while the opposite was true for Cluster 1. Brain responses to NEU and UNP images were comparable in the two groups. In the current report, we now refer to the original Cluster 1 as P>C to designate a higher level of activation in the LPP to pleasant vs cigarette pictures; while Cluster 2 is denoted as C>P to indicate the opposite pattern.

Analysis of LPP Responses within Treatment Group

LPP group membership (P>C vs. C>P) was originally determined from the cluster solution model presented in our previous report (Versace et al. 2012) and was assigned prior to medication. For this report, we sought to verify that the differential reactivity to CIG and PLE pictures observed between the LPP groups in the aggregate sample was present within each

medication group prior to the start of treatment. We conducted an ANOVA on the 180 smokers using LPP group (P>C [n = 99] vs. C>P [n = 81]) and Treatment group (varenicline [n=58] vs. bupropion [n=59] vs. placebo [n=63]) as between-subjects factors, and picture Category (UNP, NEU, PLE, CIG) as a within-subjects factor, with the mean LPP amplitude (between 400 and 700 ms after picture onset) serving as the dependent variable. We tested the 3-way interaction (LPP Group × Treatment Group × Picture Category) to determine if the LPP responses to picture categories differed as a function of LPP and medication treatment groups. We found no significant LPP group × treatment group × picture category interaction ($F_{(6, 522)} = 1.3306$, $p = .24153$). However, we verified a significant LPP group × picture category interaction within the varenicline ($F_{(3, 168)} = 11.104$, $p < .000001$); bupropion ($F_{(3, 171)} = 18.027$, $p < .000001$) and placebo ($F_{(3, 183)} = 16.488$, $p < .000001$) groups, thus recapitulating the results seen in the aggregate sample from our previous report (Versace et al. 2012). The LPP for PLE pictures was higher than CIG pictures for those classified as P>C (all F's > 49; $p < 0.00001$); and higher for CIG than PLE for the C>P group (all F's > 16; $p < 0.0005$), within each of the treatment groups (See Supplement Figure1). No such differences were noted for UNP and NEU picture types (data not shown) as indicated in our original analysis of the aggregate data.

Assessment of Abstinence

Abstinence data was collected at all contacts using a timeline follow-back (TLFB) procedure (Brown et al. 1998, Law et al. 2003). Abstinence outcomes conformed to the Society of Research on Nicotine and Tobacco (SRNT) guidelines (Hughes et al. 2003). In this study, as in the main clinical outcome paper (Cinciripini et al. 2013), *prolonged abstinence* at the end of treatment (EOT), and 3- and 6- months post-quit served as our primary smoking outcome measure. The common starting point for assessing prolonged abstinence was the end of the grace

period (i.e., 2 weeks following the quit date). For prolonged abstinence, relapse was defined by 7 or more consecutive days of smoking or smoking at least 1 cigarette over two consecutive weeks from the end of the grace period to a selected future time point (Hughes et al. 2003).

Other measures of abstinence were also assessed and included: 1) seven-day point prevalence (no smoking in the 7 days prior to assessment (e.g., EOT, 3 and 6- months post-quit date); 2) Continuous Abstinence (2-week grace) which was defined as no smoking, from 2 weeks past the quit-date (grace period) to a future time point; 3) Continuous Abstinence (FDA) was defined as no smoking over the last 4 weeks of treatment, or between weeks 8 and 12 in this trial. This measure provides comparability to the results of the phase-3 trials for varenicline and other pharmacotherapies where continuous abstinence over the last four weeks of treatment served as the primary criteria for measuring efficacy and obtaining FDA approval for the pharmacotherapy.

In-person reports of abstinence were verified by expired CO < 10 ppm. Abstinent participants at the 3 and 6 month post-quit visits who could not return to the clinic and those reporting abstinence at the 4^{th} (EOT) and 5^{th} phone session were asked to provide a saliva cotinine sample by mail. Values of salivary cotinine of < 15 ng/ml were considered abstinent. Participants unavailable for assessment were considered non-abstinent.

SUPPLEMENTARY TABLES

Table S1. Bayesian and Frequentist (Maximum Likelihood) Estimates of the Interaction of LPP group[1] and Treatment for Prolonged Abstinence at the End of Treatment.

	Bayesian Posterior Parameter Estimates			Maximum Likelihood Parameter Estimates		
Parameter	Odds Ratio	95% Credible Limits		Odds Ratio	Wald 95% Confidence Limits	
Intercept	0.251	0.091	0.584	0.261	0.106	0.641
Varenicline	3.770	1.249	12.643	3.608	1.167	11.151
Bupropion	1.365	0.326	5.559	1.369	0.351	5.335
P>C	1.631	0.511	5.604	1.597	0.499	5.108
Varenicline*P>C[1]	0.831	0.166	4.096	0.847	0.177	4.039
Bupropion*P>C	2.322	0.425	13.286	2.240	0.424	11.848

Note. Parameter values this analysis are presented for purposes of comparison of the Frequentist and Bayesian methods, using the primary outcome of prolonged abstinence at the end of treatment as defined in the parent clinical trial. For analyses of other time points, abstinence definitions or efficacy/effectiveness analyses, with vague, neutral or informative, skeptical priors are available from the authors on request. [1]LPP Group: P>C refers to smokers with higher LPP responses to pleasant than to cigarette-related stimuli; C>P refers to the smokers with higher brain responses to cigarette-related than pleasant stimuli.

Table S2. Bayesian Posterior Distributions: Probability Estimates for Interactions of LPP Group[1] and Treatment for Efficacy and Comparative Effectiveness.

	Standard Efficacy Parameterization (Reference Placebo and C>P)				Comparative Effectiveness Parameterization (Reference Bupropion and C>P)	
	Varenicline x LPP Group Interaction p(Interaction)		Bupropion x LPP Group Interaction p(Interaction)		Varenicline x LPP Group Interaction p(Interaction)	
Abstinence Type and Time Point	Vague, Neutral Priors	Skeptical, Informative Priors	Vague, Neutral Priors	Skeptical, Informative Priors	Vague, Neutral Priors	Skeptical, Informative Priors
Prolonged at EOT	0.590	0.538	0.835	0.745	0.895	0.713
Prolonged at 3 months	0.641	0.569	0.896	0.852	0.956	0.571
Prolonged at 6 months	0.742	0.642	0.678	0.596	0.875	0.641
Continuous (FDA) at EOT	0.690	0.538	0.639	0.658	0.826	0.669
Continuous (FDA) at 3 months	0.576	0.530	0.801	0.717	0.880	0.530
Continuous (FDA) at 6 months	0.598	0.501	0.733	0.578	0.676	0.500
Continuous (Grace) to EOT	0.596	0.543	0.850	0.782	0.919	0.543
Continuous (Grace) at 3 Months	0.531	0.509	0.885	0.824	0.924	0.514
Continuous (Grace) at 6 months	0.601	0.501	0.736	0.578	0.677	0.501
Seven Day Point Prevalence at EOT	0.599	0.509	0.583	0.504	0.513	0.501
Seven Day Point Prevalence at 3 months	0.528	0.506	0.692	0.571	0.723	0.509
Seven Day Point Prevalence at 6 months	0.791	0.702	0.784	0.708	0.945	0.705

Note. EOT=end of treatment. P>C refers to smokers with higher LPP responses to pleasant than to cigarette-related stimuli; C>P refers to the smokers with higher brain responses to cigarette-related than pleasant stimuli [1] LPP Group: P>C refers to smokers with higher LPP responses to pleasant than to cigarette-related stimuli; C>P refers to the smokers with higher brain responses to cigarette-related than pleasant stimuli.

Table S3. Summary of the Probabilities of the Simple Effects for the Efficacy Analysis.

	Odds Ratio	95% CBI LCL	95% CBI UCL	p(Odds Ratio > 1)
Prolonged at EOT				
P>C: Varenicline	2.151	1.069	9.738	0.981
Bupropion	2.254	1.214	8.593	0.991
C>P: Varenicline	3.784	1.248	12.776	0.991
Bupropion	1.369	0.326	5.604	0.670
Prolonged at 3 months				
P>C: Varenicline	3.155	1.079	9.825	0.982
Bupropion	2.864	1.099	7.733	0.985
C>P: Varenicline	4.252	1.354	15.436	0.994
Bupropion	0.866	0.150	4.296	0.430
Prolonged at 6 months				
P>C: Varenicline	2.630	0.876	8.161	0.957
Bupropion	1.627	0.602	4.552	0.829
C>P: Varenicline	4.759	1.248	24.354	0.990
Bupropion	0.965	0.104	7.011	0.486
Continuous (FDA) at EOT				
P>C: Varenicline	3.665	1.207	11.853	0.989
Bupropion	3.203	1.188	9.229	0.990
C>P: Varenicline	5.630	1.673	23.338	0.998
Bupropion	2.319	0.509	11.373	0.863
Continuous (FDA) at 3-months				
P>C: Varenicline	3.718	1.195	12.453	0.989
Bupropion	3.826	1.395	11.546	0.996
C>P: Varenicline	4.361	1.276	18.017	0.991
Bupropion	1.687	0.335	8.500	0.741
Continuous (FDA) at 6-months				
P>C: Varenicline	3.232	0.991	11.569	0.974
Bupropion	1.992	0.666	6.484	0.890
C>P: Varenicline	2.508	0.597	13.394	0.893
Bupropion	0.968	0.103	7.033	0.487
Continuous (Grace) at EOT				
P>C: Varenicline	3.105	1.026	9.966	0.978
Bupropion	3.208	1.199	9.265	0.990
C>P: Varenicline	3.813	1.113	15.854	0.984
Bupropion	1.146	0.191	6.302	0.563
Continuous (Grace) at 3 months				
P>C: Varenicline	3.152	0.998	10.665	0.975
Bupropion	3.841	1.391	11.680	0.996
C>P: Varenicline	3.329	0.954	13.906	0.970
Bupropion	1.149	0.189	6.211	0.564
Continuous (Grace) at 6 months				
P>C: Varenicline	3.233	0.989	11.568	0.974
Bupropion	1.994	0.660	6.564	0.889
C>P: Varenicline	2.511	0.596	13.453	0.892
Bupropion	0.968	0.104	7.037	0.487
Seven Day Point Prevalence at EOT				
P>C: Varenicline	4.662	1.561	15.168	0.997
Bupropion	2.740	1.064	7.333	0.981
C>P: Varenicline	3.795	1.257	12.738	0.991
Bupropion	2.299	0.613	9.046	0.892
Seven Day Point Prevalence at 3 months				
P>C: Varenicline	3.576	1.215	11.266	0.990

	Odds Ratio	95% CBI LCL	95% CBI UCL	p(Odds Ratio > 1)
Bupropion	2.099	0.830	5.456	0.941
C>P: Varenicline	3.782	1.245	12.681	0.991
Bupropion	1.366	0.325	5.534	0.670
Seven Day Point Prevalence at 6 months				
P>C: Varenicline	1.917	0.643	5.846	0.878
Bupropion	1.556	0.643	5.846	0.814
C>P: Varenicline	3.813	1.112	15.822	0.984
Bupropion	0.675	0.076	4.166	0.340

Note. The reference group is placebo. Odds ratio and 95% Credible Interval (CBI) upper (UCL) and lower (LCL) confidence limits. The credible intervals estimate the relative probabilities that the parameter estimates fall within this range. EOT=end of treatment. P>C refers to smokers with higher LPP responses to pleasant than to cigarette-related stimuli; C>P refers to the smokers with higher brain responses to cigarette-related than pleasant stimuli.

Table S4. Summary of the Probabilities of the Simple Effects for the Comparative Effectiveness Analysis.

	Odds Ratio	95% CBI LCL	95% CBI UCL	p(Odds Ratio > 1)
Prolonged at EOT				
P>C: Varenicline v. Bupropion	1.000	0.363	2.298	0.498
C>P: Varenicline v. Bupropion	2.815	0.826	10.527	0.950
Prolonged at 3-months				
P>C: Varenicline v. Bupropion	1.108	0.403	3.077	0.578
C>P: Varenicline v. Bupropion	5.089	1.262	25.562	0.990
Prolonged at 6-months				
P>C: Varenicline v. Bupropion	1.615	0.578	4.571	0.819
C>P: Varenicline v. Bupropion	5.261	1.055	38.671	0.980
Continuous (FDA) at EOT				
P>C: Varenicline v. Bupropion	1.141	0.417	3.159	0.601
C>P: Varenicline v. Bupropion	2.443	0.726	9.283	0.924
Continuous (FDA) at 3-months				
P>C: Varenicline v. Bupropion	0.963	0.349	2.661	0.470
C>P: Varenicline v. Bupropion	2.594	0.722	11.170	0.926
Continuous (FDA) at 6-months				
P>C: Varenicline v. Bupropion	1.627	0.558	4.738	0.816
C>P: Varenicline v. Bupropion	2.595	0.141	9.391	0.868
Continuous (Grace) at EOT				
P>C: Varenicline v. Bupropion	0.966	0.349	2.662	0.475
C>P: Varenicline v. Bupropion	3.327	0.847	17.493	0.956
Continuous (Grace) at 3-months				
P>C: Varenicline v. Bupropion	0.819	0.295	2.258	0.351
C>P: Varenicline v. Bupropion	2.905	0.727	15.304	0.932
Continuous (Grace) at 6-months				
P>C: Varenicline v. Bupropion	1.623	0.560	4.733	0.815
C>P: Varenicline v. Bupropion	2.582	0.511	20.903	0.867
Seven Day Point-Prevalence at EOT				
P>C: Varenicline v. Bupropion	1.695	0.600075	5.053	0.837
C>P: Varenicline v. Bupropion	1.655	0.519598	5.558	0.801
Seven Day Point-Prevalence at 3 months				
P>C: Varenicline v. Bupropion	1.701	0.598	5.079	0.840
C>P: Varenicline v. Bupropion	2.768	0.827	10.557	0.949
Seven Day Point-Prevalence at 6 months				
P>C: Varenicline v. Bupropion	1.232	0.440	3.432	0.654
C>P: Varenicline v. Bupropion	5.668	1.223	43.913	0.988

Note. Odds ratio and 95% Credible Interval (CBI) upper (UCL) and lower (LCL) confidence limits. The credible intervals estimate the relative probabilities that the parameter estimates fall within this range. EOT=end of treatment. P>C refers to smokers with higher LPP responses to pleasant than to cigarette-related stimuli; C>P refers to the smokers with higher brain responses to cigarette-related than pleasant stimuli.

SUPPLEMENTARY FIGURES

Figure S1. Cluster Solution for LPP's. Scatter plot for individual values of the LPP to pleasant (Y-axis) and cigarette (X-axis) stimuli by LPP group (P>C; C>P),

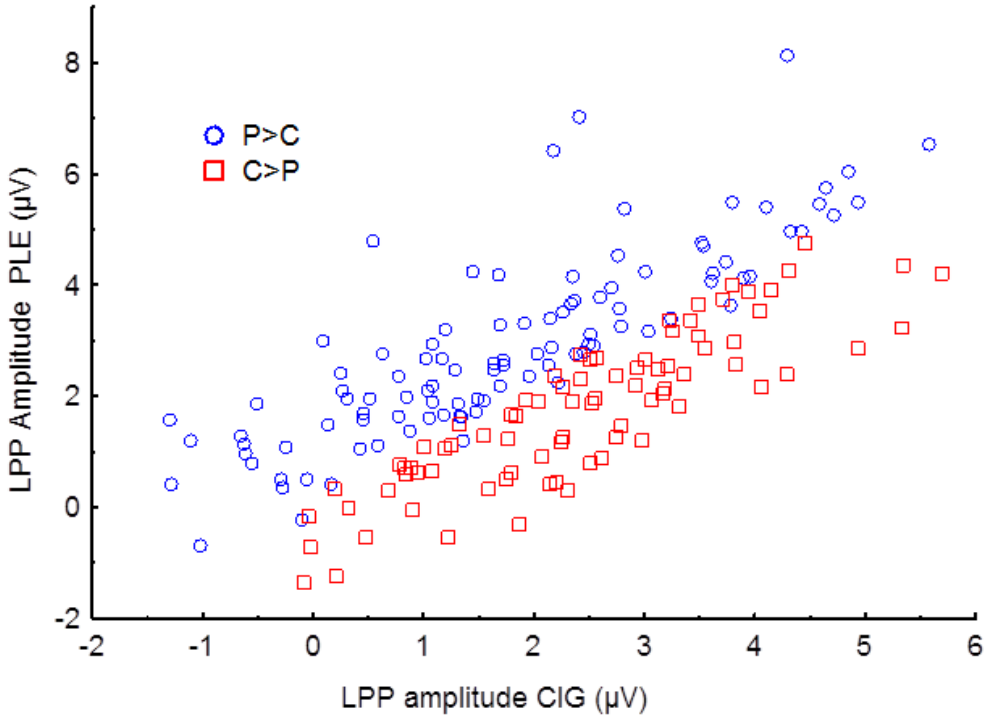


Figure S2. Mean pre-treatment late positive potential (LPP) magnitude (microvolts) of the 4 picture categories as a function of medication group assignment and original LPP group (P>C and C>P). A significant reward sensitivity group by picture category interaction was noted within the varenicline ($F_{(3, 168)}$ =11.104, p=.00000); bupropion ($F_{(3, 171)}$ =18.027, p=.00000) and placebo ($F_{(3, 183)}$ =16.488, p=.00000) groups. Differences between groups were noted for CIG vs. PLE pictures. Within each of the treatment groups, the LPP to CIG pictures was lower than the LPP to PLE pictures for those classified as CRS- (all F's > 49; p < 0.00001); and higher for CIG than PLE for the CRS+ group (all F's > 16; p < 0.0005). No such differences were noted for UNP and NEU pictures, as indicated in our original analysis of the aggregate data (data not shown).

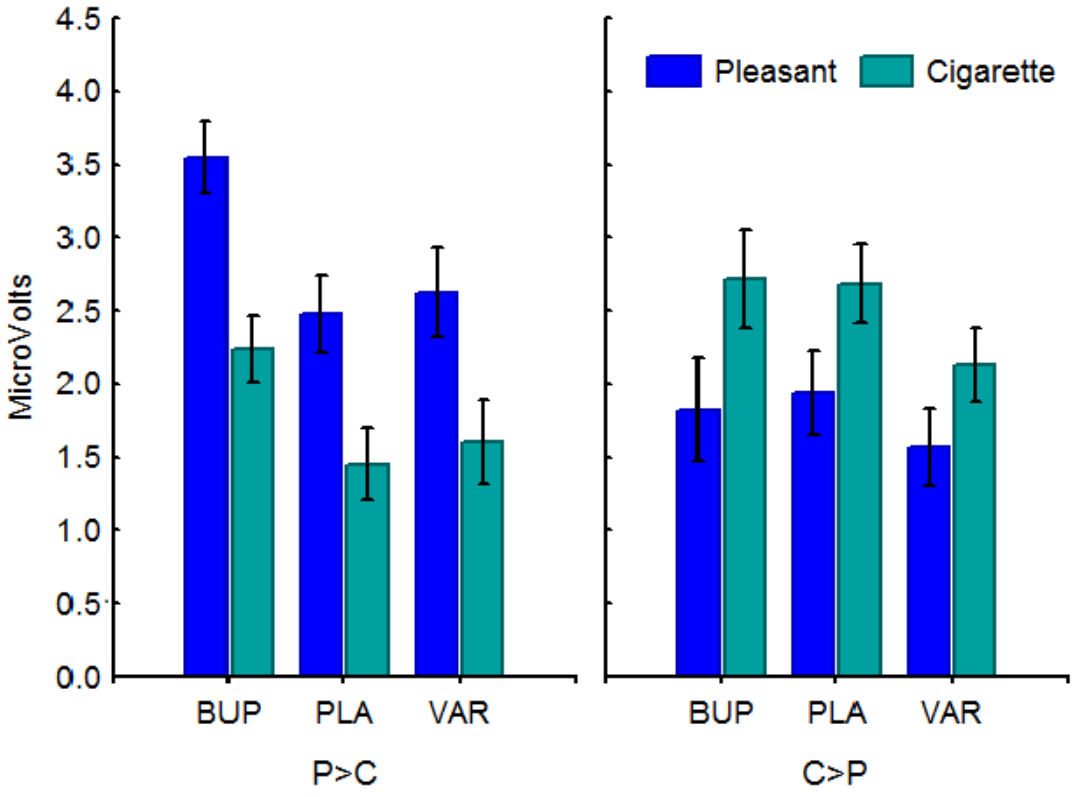


Figure S3. Efficacy Analysis for Prolonged Abstinence at end of treatment (EOT). Posterior distributions for the parameters estimates of Bupropion x LPP Group and Varenicline x LPP Group with Placebo as the reference condition. The dashed line depicts the null hypothesis (i.e., odds ratio associated with the interaction term = 1), and the probability of each interaction is the area under the curve above an odds ratio = 1.0.

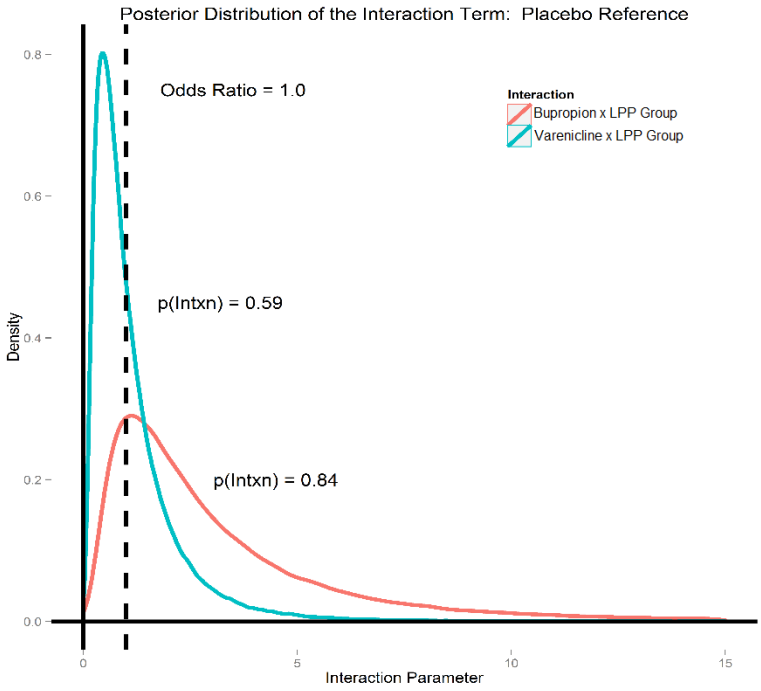


Figure S4. Comparative Effectiveness Analysis of Prolonged Abstinence at end of treatment (EOT). Posterior distribution for the parameter estimate of Varenicline x LPP Group interaction with bupropion as the reference condition. The dashed line depicts the null hypothesis (i.e., odds ratio associated with the interaction term = 1), and the probability of the interaction is the area under the curve above an odds ratio = 1.0.

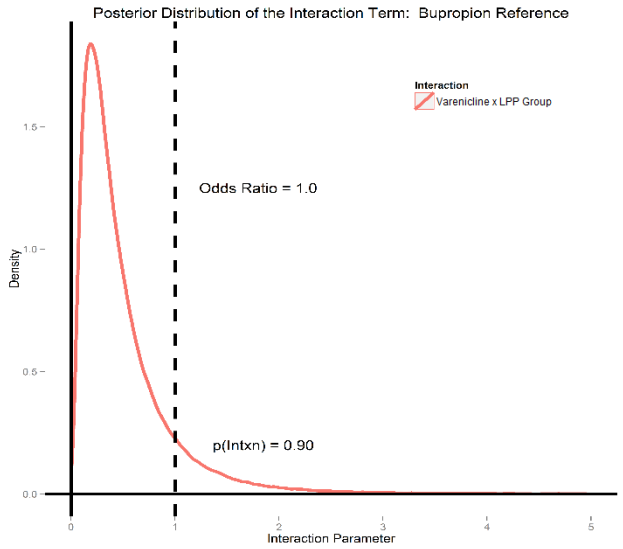


Figure S5: Efficacy Analysis for Prolonged Abstinence at end of treatment (EOT). Posterior distributions for the parameters estimates of the simple effects of bupropion and varenicline relative to placebo within LPP Group P>C. The dashed line depicts the null hypothesis (i.e., odds ratio associated with the interaction term = 1), and the probability of each simple effect is the area under the curve above an odds ratio = 1.0.

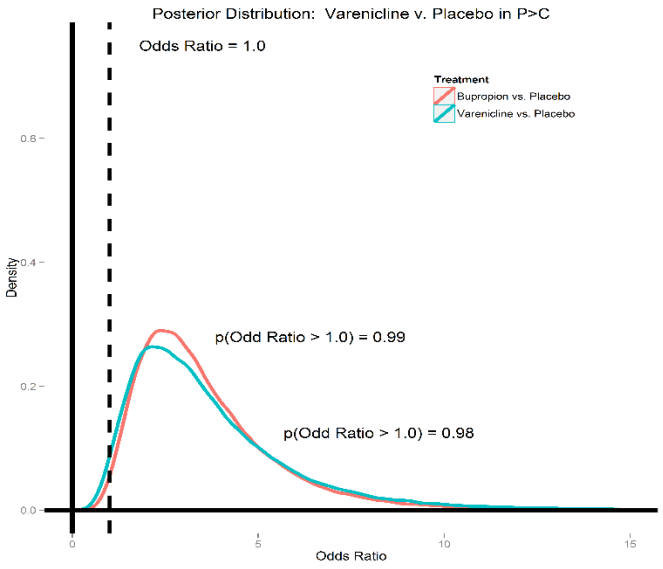


Figure S6: Efficacy Analysis for Prolonged Abstinence at end of treatment (EOT). Posterior distributions for the parameters estimates of the simple effects of Bupropion and Varenicline relative to Placebo within LPP group C>P. The dashed line depicts the null hypothesis (i.e., odds ratio associated with the interaction term = 1), and the probability of each simple effect is the area under the curve above an odds ratio = 1.0.

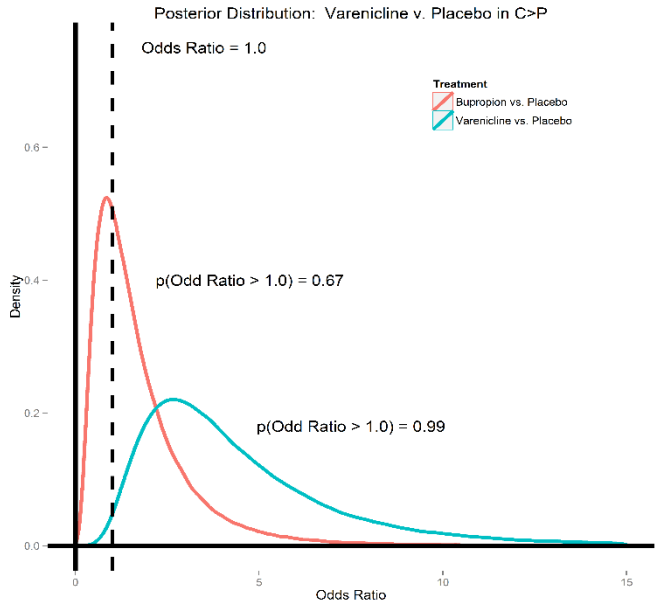
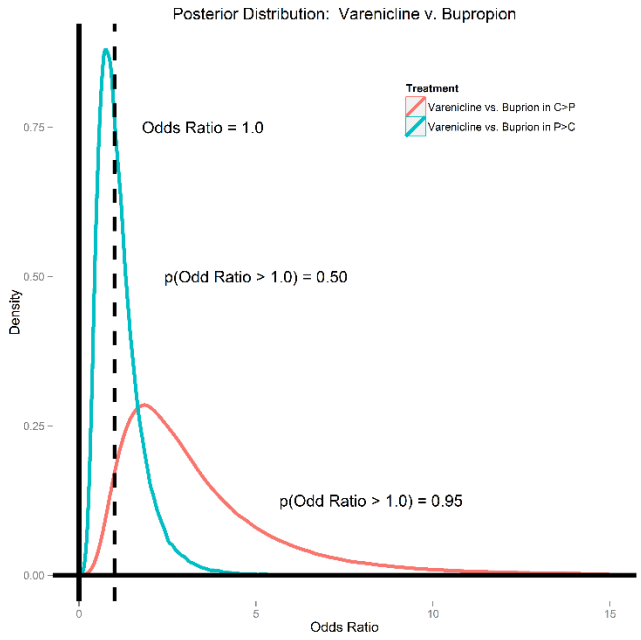


Figure S7. Comparative Effectiveness Analysis for Prolonged Abstinence at end of treatment (EOT). Posterior distributions for the parameters estimates of the simple effect of Varenicline relative to Bupropion within each LPP Group (C>P;P>C). The dashed line depicts the null hypothesis (i.e., odds ratio associated with the interaction term = 1), and the probability of each simple effect is the area under the curve above an odds ratio = 1.0.



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