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Predictors of Neuropsychiatric Adverse Events with Smoking Cessation Medications in the Randomized Controlled EAGLES Trial

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Abstract

Background—Pre-treatment factors that increase smokers' risk of experiencing neuropsychiatric adverse events (NPSAEs) when quitting smoking are unknown.

Objective—Identify baseline smoker characteristics beyond history of mental illness that predict which participants were more likely to experience moderate-to-severe NPSAEs in EAGLES (ClinicalTrials.gov: NCT01456936).

Design—Prospective correlational study in context of a double-blind, randomized trial.

Setting—140 centers, multinational.

Participants—Smokers without (N=3984)/with (N=4050) histories of, or current clinically stable, psychiatric disorders.

Interventions—Bupropion, 150 mg twice-daily, or varenicline, 1 mg twice-daily, versus active control (nicotine patch, 21 mg/day with taper) and placebo for 12 weeks with 12-week non-treatment follow-up.

Measurements—Primary safety outcome was the incidence of a composite measure of moderate/severe NPSAEs. Associations among baseline demographic/clinical characteristics and the primary safety endpoint were analyzed *post-hoc* via generalized linear regression.

Results—Smokers of White race, those who reported prior suicidal ideation and/or behavior, and those with current symptoms of anxiety were more likely to experience clinically significant NPSAEs when trying to quit, whether they had a psychiatric diagnosis or not. Among smokers with psychiatric disorders, younger age, female sex, history of substance use disorders, and proxy measures of nicotine dependence or psychiatric illness severity also predicted greater risk. There were no significant interactions between these characteristics and treatment.

Limitations—Smokers with unstable psychiatric disorders or with current, active substance use disorders were excluded.

Conclusion—Irrespective of cessation pharmacotherapy use, smokers attempting to quit were more likely to experience moderate-to-severe NPSAEs if they reported current anxiety or prior

suicidal ideation at baseline and were White. In smokers with a psychiatric history, female sex, younger age, and greater severity of nicotine dependence were also predictive.

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INTRODUCTION

The large, multinational, Evaluating Adverse Events in a Global Smoking Cessation Study (EAGLES; NCT01456936) (1) found that ~4% of smokers experienced a clinically significant neuropsychiatric adverse event (NPSAE) during a quit attempt regardless of the medication to which they were assigned: transdermal nicotine patch (nicotine replacement therapy, NRT), bupropion, varenicline, or placebo. NPSAE incidence across active treatments was not significantly different from placebo. Incidence varied significantly by cohort: ~2% of smokers without a history of a psychiatric disorder (non-psychiatric cohort, NPC) reported clinically significant NPSAEs, compared with ~6% of smokers with current stable or past psychiatric disorders (psychiatric cohort, PC). However, little is known about patient-level characteristics or disease-related factors that predict which smokers are more likely to experience clinically significant NPSAEs when trying to quit. Identifying such pre-existing factors might help clinicians anticipate which smokers are at heightened risk and modify treatment accordingly.

Studies evaluating predictors of AEs with smoking cessation pharmacotherapies are sparse. The largest study in transdermal nicotine patch users found that successfully quitting smoking and female sex predicted sleep disturbances, and that application site reactions were associated with other skin conditions, younger age, female sex, and other demographic characteristics (2). Given that some neuropsychiatric side effects from pharmacotherapy might overlap with symptoms of nicotine withdrawal, it is relevant that several studies have evaluated predictors of withdrawal and found that changes in mood states such as anhedonia (3), negative affect (4) and anxiety (5,6), and severity of nicotine dependence (7) are associated with nicotine withdrawal symptom expression. However, no study has examined NPSAEs among smokers in depth, and none have compared the relative risk across all three front-line medications and placebo in smokers with and without psychiatric conditions until now.

The purpose of this secondary analysis was to examine baseline characteristics associated with the trial's primary composite safety endpoint to determine potential predictors of clinically significant NPSAEs in participants from EAGLES. In models that considered whether the treatments themselves were associated with such adverse outcomes, we explored whether demographic and clinical characteristics of the smokers, smoking-related variables, and mental health-related characteristics were associated with these adverse effects.

METHODS

Design Overview

EAGLES was a phase 4, multinational, multicenter, randomized, double-blind, triple-dummy, active- (NRT) and placebo-controlled trial of varenicline and bupropion for 12 weeks with 12-week non-treatment follow-up conducted between November 2011 and January 2015, at 140 centers in 16 countries (1). Details of the methods were described previously (1).

The institutional review boards at participating institutions approved consent forms and the study procedures (the study protocol is available at http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(16)30272-0/abstract). The study adhered to the Declaration of Helsinki (8) and the International Conference on Harmonisation Good Clinical Practice Guidelines (9). An independent Data Monitoring Committee reviewed safety data at pre-specified time points to ensure participant safety.

Setting and Participants

Eligible participants were men and women aged 18–75 years, who smoked an average of ≥10 cigarettes per day during the prior year and during the month before the screening visit, had an

exhaled carbon monoxide (CO) >10 parts per million (ppm) at screening, and who were motivated to stop smoking. All participants provided informed consent. Participants included in the NPC had no history of *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)* (10) Axis I disorders. Included in the PC were participants with a primary diagnosis of mood disorders (major depression, bipolar I or bipolar II disorder), anxiety disorders (panic disorder with or without agoraphobia, post-traumatic stress disorder, obsessive-compulsive disorder, social phobia, generalized anxiety disorder), psychotic disorders (schizophrenia, schizoaffective disorder), or borderline personality disorder meeting the *DSM-IV-TR* (10) criteria confirmed by the Structured Clinical Interviews for DSM-IV-TR Axis I & II Disorders (SCID-I & -II) (11,12). PC participants were clinically stable (i.e., no exacerbations of their condition in the prior 6 months; if on treatment, treatment was stable for at least 3 months, with no treatment change anticipated during the study) and not judged to be at high risk of self-injurious or suicidal behavior. Psychiatric comorbidities were allowed if not considered severe enough to compromise study participation. Participants with a primary diagnosis of borderline personality disorder were not included in the present analysis owing to the small size of the group not allowing proper statistical modeling. All other participants who were randomized and received at least one dose of study treatment were included in the analysis.

Randomization and Interventions

Participants were assigned to one of the two cohorts (PC or NPC) on the basis of SCID results, with equal cohort sizes planned. They were then randomized in a 1:1:1:1 ratio using a computer-generated schedule to receive varenicline 1 mg twice daily, bupropion 150 mg twice daily, NRT 21 mg per day with taper, or placebo for 12 weeks with a 12-week non-treatment follow-up.

Treatment compliance was ~80% across the four treatments. Participants were encouraged to complete all study visits even if treatment was discontinued.

Outcomes and Follow-up

The pre-specified primary outcome for EAGLES was also the outcome for this *post-hoc* secondary analysis and was defined as a composite measure of moderate to severe NPSAEs developed with input from the U.S. Food and Drug Administration. The endpoint was operationalized by coding AEs reported by the investigators to preferred terms (PTs) in the Medical Dictionary for Regulatory Activities (MedDRA) and by further mapping those PTs in a pre-defined way to 16 NPS symptom categories included in the composite measure. In addition, NPSAEs (new events or increases in severity of ongoing symptoms) had to occur during treatment or within 30 days of treatment discontinuation and had to meet pre-established severity criteria to be included in the outcome. NPSAEs were required to be severe (significant interference with subject's usual daily functioning) for four of the 16 components (anxiety, depression, feeling abnormal, or hostility). The remaining 12 (agitation, aggression, delusions, hallucinations, homicidal ideation, mania, panic, paranoia, psychosis, suicidal ideation [SI], suicidal behavior [SB], or suicide, including suicidal depression) had to be rated as either moderate (some interference) or severe.

NPSAEs and Psychiatric Rating Scales

At baseline, cigarette dependence severity was assessed with the Fagerström Test for Cigarette Dependence (FTCD) (13), and trait aggression was measured using the Buss-Perry Aggression Questionnaire (BPAQ) (14). The Columbia-Suicide Severity Rating Scale (C-SSRS) (15) and the Hospital Anxiety and Depression Scale (HADS) (16), a self-reported inventory that measures both anxiety (seven items) and depressive symptoms (seven items), were administered at baseline and all study visits to assess aspects of psychiatric symptom severity.

In addition, at all study visits, trained interviewers elicited the emergence of NPSAEs with open-ended questions, direct observation, and a semi-structured Neuropsychiatric Adverse Events Interview (NAEI) (1,17). Investigators then evaluated whether positive responses from these interviews, as well as on the C-SSRS and from any proxy reports from subjects' family members or physicians, were NPSAEs.

Statistical Analysis

The baseline covariates examined in this secondary analysis were a combination of categorical and numerical measures: 1) demographic and clinical characteristics including age, sex, race (White, Black, Other), and body mass index (BMI); 2) smoking-related characteristics including severity of cigarette dependence (FTCD), age at onset of regular smoking, and prior use of smoking cessation study medications (no or any for each of the three medications); and 3) mental health-related measures including having any type of comorbid psychiatric diagnosis, a history of an alcohol or other substance use disorder, HADS anxiety subscale score, HADS depression subscale score, lifetime SI or SB as captured by C-SSRS, trait aggression as measured by the BPAQ, and use of psychotropic medications including sleeping aids. Within the PC, primary subcohort membership (i.e., primary mood, anxiety, or psychotic disorder) was also analyzed as a covariate.

Associations among covariates and the primary composite NPSAE outcome were analyzed with a sequential approach via generalized linear regression. For continuous covariates a quadratic relationship was also investigated. As established in the main EAGLES outcome paper (1), a primary psychiatric diagnosis was a strong predictor of NPSAEs, and therefore the additional predictors of NPSAE were analyzed within the NPC and PC separately. Covariates and their by-treatment interactions deemed significant via a screening assessment—model controlling for

treatment (NRT, bupropion, varenicline, and placebo) and region (U.S. versus non-U.S.)—were subsequently included in a stepwise regression analysis that determined those covariate terms contributing to the rate of NPSAE.

Role of the Funding Source

EAGLES was a post-marketing requirement in the U.S. and Europe for Pfizer and GlaxoSmithKline. Sponsor employees, with input from academic authors, designed the study. The sponsors supported the conduct of the trial, monitored study sites, and collected and analyzed the data. All authors had full access to the data. The lead academic (corresponding) author (RMA) prepared the initial draft of the manuscript and had final responsibility for the decision to submit for publication.

RESULTS

Figure 1 is a modified, abridged version of the CONSORT flow diagram presented in the primary manuscript (1). It differs in that 24 participants in the original PC sample with primary diagnoses of borderline personality disorder were excluded in this secondary analysis owing to the small sample size and modeling interference of this group; these individuals also did not report any primary endpoint NPSAEs. Overall, study discontinuation rates were similar across treatment groups during both the active treatment phase (NPC=14.6%; PC=15.4%) and the 12-week non-treatment follow-up period (NPC=7.0%; PC=6.7%).

Baseline Characteristics

Baseline demographic, smoking history, and psychiatric characteristics of the 8034 participants included in the present secondary analysis are illustrated in Table 1. As reported previously, baseline characteristics were similar across treatment groups but there were differences between the two cohorts (1). Those enrolled in the PC were more likely to be women, be

recruited from sites within the U.S., and have higher levels of cigarette dependence. More than one third of those enrolled in the PC met the DSM-IV-TR criteria for a comorbid psychiatric disorder, and 23% had a history of an alcohol or other substance use disorder. As expected, baseline HADS anxiety and depression subscale scores were higher in PC smokers than smokers without psychiatric disorders, and the PC group reported prior histories of SI and/or SB that were more than seven-fold greater than NPC smokers.

Predictors of NPSAEs in the PC

Table 2 illustrates the regression results of the screening assessment of predictors in the PC. Twelve of the 17 predictor variables (see bolded) were significantly associated with an increased rate of occurrence of the primary NPSAE endpoint. These included demographic/clinical characteristics (younger age, female sex, White versus Black race, and greater BMI), smoking-related variables (higher level of cigarette dependence, prior bupropion use, and prior NRT use), and mental health-related characteristics (psychiatric comorbidity, past history of substance use disorder, elevated HADS anxiety score, lifetime history of SI/SB, and higher trait aggression). The table also shows the magnitude of the effect of the predictor and, if the predictor is a significant continuous variable (e.g., age), the change in units to yield a 1.0% increase in the chance of a clinically significant NPSAE. Primary psychiatric disorder diagnostic category (e.g., mood, anxiety, or psychotic disorder) as determined by the SCID-I was not significantly associated with NPSAEs.

The significant covariates specified above were entered in a stepwise final regression analysis to identify those predictor variables that independently contributed to the NPSAE rate. As illustrated in Table 3, seven predictors were retained in the model including younger age, female sex, prior use of bupropion, prior NRT use, history of a substance use disorder, higher HADS anxiety score, and lifetime history of SI/SB.

Predictors of NPSAEs in the NPC

In contrast to the large number of variables found to be associated with an increased occurrence of clinically significant NPSAEs in the PC, Table 4 shows that in the NPC, only three factors were significantly associated with the primary safety endpoint, a result confirmed in the final regression model (see Table 5). Notably, these three factors—higher HADS anxiety scale score, endorsing a prior history of SI/SB, and White race—were consistently associated with increased NPSAE risk in both cohorts in the screening assessment (bolded in Tables 2 and 4 for emphasis).

There were no significant treatment-by-covariate interactions in either cohort.

DISCUSSION

Regardless of a smoker's psychiatric history, being more anxious at treatment onset, having a history of prior SI or SB, and being of White race were independently associated with an increased risk of experiencing a clinically significant NPSAE during a medication- or placebo-assisted quit attempt. Among smokers with histories of or current mental health conditions, risk for experiencing a moderate to severe NPSAE was also associated with female sex, younger age, a history of a substance use disorder, and prior treatment with either NRT or bupropion. Importantly, the risk for developing clinically significant NPSAEs was not associated with any treatment or particular category of psychiatric disorder, nor were there interactions among any of the treatments and the independent variables tested in our models.

Comparing our results with related studies obtained via a literature search through August 2017 adds much new information to the field. To our knowledge, this is the first report that identifies easily obtainable patient-level and mental health-related characteristics, with the potential to

help predict who is at heightened risk to experience moderate to severe NPSAEs among smokers making a quit attempt. Its uniqueness stems from the fact that EAGLES was designed precisely to evaluate such adverse effects and used both semi-structured diagnostic interviews (e.g., SCID-I & -II) and validated, reliable assessment tools (C-SSRS and HADS) to obtain baseline clinical characteristics that could be used to retrospectively predict NPSAEs. While the literature preceding EAGLES has tracked the occurrence of serious AEs (18-21), those more narrowly defined outcomes span multiple organ systems and lack both the sensitivity and specificity of our NPSAE evaluation battery.

Three characteristics, two of which were related to smokers' mental functioning, were found to have the greatest predictive potential regardless of the individual's psychiatric history. Having a prior history of SI or SB was associated with a 4.4% increase in the rate of the primary NPSAE endpoint among smokers in the PC, and with a 4.1% increase among smokers in the NPC after controlling for other factors. While some of this association may be explained by the fact that EAGLES' primary safety endpoint included SI and there was intensive monitoring of such events during the trial with the C-SSRS, this finding is important. That smoking and suicidal thinking and behaviors are linked is well established (22-24). However, our finding that past SI/SB predicts the likelihood of one experiencing a serious NPS adverse effect during a medication-assisted quit attempt is novel. Moreover, that prior history of SI/SB was independently associated with elevated risk—even after considering other factors such as measures of cigarette addiction itself or of psychiatric illness-related characteristics—speaks to the potential value of obtaining such a history in all smokers who are attempting to quit smoking.

Even subtle elevations in anxiety symptoms at baseline were also found to predict increased occurrence of clinically significant NPSAEs in smokers with and without psychiatric disorders. Thus, for every 3.9 units increase in HADS anxiety subscale scores among PC smokers, or 4.0

units increase among NPC participants, absolute risk of occurrence of the NPSAE endpoint was increased by 1%. The HADS anxiety subscale scoring ranges from 0 to 21 units with each of the seven scale items scored from 0 (no symptom present) to 3 (markedly present). While mean HADS anxiety scores in the EAGLES participants were in the normal range (0–7 units), PC group participants had higher mean HADS scores than NPC smokers. Also, the ~4 unit elevation observed that signaled increased NPSAE risk may have been linked to some of these smokers having HADS anxiety scores in the 8–10 units range (suggestive of an anxiety state), or ≥11 units, which is the cut-off score marking the probable presence of some type of anxiety disorder. That the increased HADS score predicted adverse effects, while a diagnosis of a frank Axis I anxiety disorder was not associated with increased risk, indicates that a smoker's current anxiety state prior to making a quit attempt may be a more relevant predictor, and that anxiety is a symptom which spans multiple psychiatric and medical disorders. While, to our knowledge, this is the first report of anxiety symptoms being linked to smokers experiencing AEs during a medication-assisted quit attempt, it is noteworthy that patients' anxiety levels have been linked to severity of nicotine withdrawal (5,6) and to increased likelihood of AEs in patients taking antidepressant (25,26) or antiepileptic medications (27,28). It is also worth noting that anxiety symptoms, and not depressive symptoms also measured on the HADS, were associated with increased risk—an observation also made with antiepileptic drug use (27).

The demographic and clinical characteristics we found to be associated with clinically significant NPSAEs varied between cohorts, with the exception of White versus Black race, which was found in both cohorts in the screening assessment but was only retained in the stepwise model among smokers in the NPC. There is little information available on how such racial/ethnic differences affect NPS safety risk, and more research on this topic is warranted. However, to the extent that quitting smoking evokes stress in some individuals (29), it is interesting to note that Whites have a more robust hypothalamic-pituitary-adrenal axis response to a psychological

stressor than Blacks (30), implying a potential neurobiological racial difference in stress reactivity. Among smokers with histories of or current mental health conditions, being younger and female was retained in the final regression model after controlling for other variables. Female sex has been linked to milder side effects such as sleep problems and application site reactions in smokers using transdermal nicotine patches (2), and both female sex and younger age have been associated with risk for adverse effects from antiepileptic drugs (27)—the only other class of medications we could find to systematically evaluate such predictors.

Variables associated with cigarette addiction itself and mental health-related factors also predicted additional unique variance in smokers with mental health conditions. Two proxy measures of cigarette dependence severity—prior use of bupropion and previous treatment with NRT—were both retained in the final regression model. The stepwise process eliminated the potentially significant FTCD as a predictor once these other variables were included. We interpret that observation cautiously, but we think it likely reflects the more severely dependent smokers being treated more often with NRT and bupropion in the past. Regarding the latter drug, it may be an artifact because our record of prior bupropion use also included use of the medication as an antidepressant. To that end, it is also noteworthy that indicators of psychiatric illness complexity, such as having a comorbid alcohol or substance use disorder, were associated with increased NPSAE occurrence. Taken together then, especially alongside the aforementioned effects of past history of SI/SB and increased state anxiety symptoms, the picture that emerges is that smokers with more complex psychiatric histories and greater severity of nicotine dependence are at greatest risk to develop clinically significant NPSAEs during a medication-assisted quit attempt.

Our study has several limitations that have been documented in detail elsewhere (1) but bear mentioning again. First, we selected a population of smokers with histories of or currently stable

mental health conditions; thus, these findings may not generalize to smokers with unstable or untreated psychiatric disorders. Second, because misuse of alcohol and other drugs causes psychiatric symptoms and mimics psychiatric syndromes (31), we excluded smokers with current substance use disorders, further limiting generalizability. Third, the frequent monitoring of this randomized clinical trial might not capture a real-world medication-assisted quit attempt. Fourth, although EAGLES is the largest placebo-controlled smoking cessation pharmacotherapy trial ever conducted, some of the subcohorts in the PC were smaller than others and power to detect effects may be limited. Fifth, EAGLES excluded individuals smoking <10 cigarettes per day, so our findings might not generalize to lighter smokers. Sixth, specific to this secondary analysis, there was no comparator involving smokers not attempting to stop. Finally, attrition occurred across all treatment arms and in both cohorts; thus, missing data could have affected the results.

In summary, regardless of cohort or the medication used, White smokers with past histories of SI and/or SB and current symptoms of anxiety were more likely to experience clinically significant NPSAEs when they tried to quit. Among smokers with psychiatric disorders, younger age, female sex, history of comorbid substance use disorders, and proxy measures of nicotine dependence or psychiatric illness severity also predicted greater NPSAE risk. While to our knowledge this is the first report of patient-level characteristics associated with clinically significant NPSAEs in smokers making a quit attempt, our findings extend those of milder AEs observed with NRT use and adverse effects linked to antidepressant and antiepileptic medication use. Although the incidence of NPSAEs is low in this clinical trial setting and unrelated to any of the study medications, awareness of these pre-existing factors in smokers is prudent as they might signal heightened NPSAE risk in individuals trying to quit smoking with and without using licensed pharmacotherapies.

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[[Legend to figure]]

Figure 1.

Participant disposition (abridged CONSORT diagram).

NPC = non-psychiatric cohort; PC = psychiatric cohort.

[[Tables]]

Table 1

Baseline Demographic, Smoking, and Psychiatric Characteristics

	NPC (N=3984)	**PC (N=4050)**
Mean age (SD), *y*	46.0 (12.9)	47.1 (11.7)
Male sex, *n (%)*	2003 (50.3)	1542 (38.1)
Race, *n (%)*		
White	3293 (82.7)	3268 (80.7)
Black	504 (12.7)	640 (15.8)
Other	187 (4.7)	141 (3.5)
Region (U.S.), *n (%)*	1875 (47.1)	2330 (57.5)
Mean BMI (SD), kg/m^2	27.6 (6.1)	28.6 (6.6)
Mean FTCD (SD)	5.5 (2.0)	6.0 (2.0)
Mean age of starting smoking (SD), *y*	17.9 (5.3)	18.5 (6.5)
Prior varenicline use, *n (%)*	576 (14.5)	687 (17.0)
Prior bupropion* use, *n (%)*	371 (9.3)	463 (11.4)
Prior NRT use, *n (%)*	994 (24.9)	1121 (27.7)
Primary psychiatric diagnosis, *n (%)*		
Mood disorder	NA	2882 (71.2)
Anxiety disorder	NA	782 (19.3)
Psychotic disorder	NA	386 (9.5)
Any comorbid psychiatric diagnosis, *n (%)*	15 (0.4)	1461 (36.1)
Alcohol/substance use disorder history, *n (%)*	8 (0.2)	932 (23.0)
Mean HADS anxiety total (SD)	2.8 (2.7)	5.2 (3.9)
Mean HADS depression total (SD)	1.5 (2.1)	3.2 (3.3)

Prior SI/SB (C-SSRS), *n (%)*	194 (4.9)	1398 (34.5)
Mean aggression score (BPAQ) (SD)	52.1 (15.4)	58.6 (18.5)
Baseline psychotropic medication, *n (%)*	356 (8.9)	2261 (55.8)

BMI = body mass index; BPAQ = Buss-Perry Aggression Questionnaire; C-SSRS = Columbia-Suicide Severity Rating Scale; FTCD = Fagerström Test for Cigarette Dependence; HADS = Hospital Anxiety and Depression Scale; NA = not applicable; NPC = non-psychiatric cohort; NRT = nicotine replacement therapy (transdermal nicotine patch); PC = psychiatric cohort; SB = suicidal behavior; SD = standard deviation; SI = suicidal ideation.

*Bupropion prior use for smoking cessation or other indications.

Table 2

Regression Results of Screening Assessment of Predictors of NPSAE (PC)

Covariate	**Increase in Rate of Primary NPSAE Endpoint, % (SE)**	***P*-value for Effect of Covariate**	***P*-value for Treatment-by-Covariate Interaction**
Age (1 year increase)	**−0.1 (0.0)**	**0.0001**	0.46
	Or 1.0% decrease per 8.5 years increase in age		
Sex (male vs female)	**–2.1 (0.7)**	**0.004**	0.26
Race			0.23
White vs Black	**2.9 (0.9)**	**0.002**	–
Other vs Black	2.7 (2.3)	0.25	–
BMI (1 unit increase)	**0.1 (0.1)**	**0.029**	0.27
	Or 1.0% increase per 7.7 units increase in BMI		
FTCD* (1 unit increase)	**0.4 (0.2)**	**0.035**	0.95
	Or 1.0% increase per 2.7 units increase in FTCD		
Age of starting smoking (1 year increase)	–0.0† (0.1)	0.34	0.13
Prior varenicline use (yes vs no)	1.6 (1.1)	0.15	0.35

Prior bupropion use (yes vs no)	**5.1 (1.5)**	**0.0005**	0.30
Prior NRT use (yes vs no)	**2.2 (0.9)**	**0.015**	0.51
Primary subcohort psychiatric diagnosis (psychotic, anxiety, mood disorders)	–[‡]	0.99	0.93
Any comorbid psychiatric diagnosis (yes vs no)	**3.3 (0.8)**	**<0.0001**	0.89
Alcohol/substance use disorder history (yes vs no)	**3.8 (1.0)**	**0.0002**	0.96
HADS anxiety total (1 unit increase)	**0.4 (0.1)**	**0.0002**	0.91
	Or 1.0% increase per 2.7 units increase in HADS anxiety total		
HADS depression total (1 unit increase)	0.2 (0.1)	0.06	0.76
Prior SI/SB [C-SSRS] (yes vs no)	**5.9 (0.9)**	**<0.0001**	0.17
Aggression score [BPAQ] (1 unit increase)[§]	0.0 (0.0)	0.63	0.66
Linear term	**0.2 (0.1)**	**0.04**	–
Quadratic term	**−0.0 (0.0)**	**0.04**	–
Baseline psychotropic medication including sleeping aids (yes vs no)	1.2 (0.7)	0.092	0.35

BMI = body mass index; BPAQ = Buss-Perry Aggression Questionnaire; C-SSRS = Columbia-Suicide Severity Rating Scale; FTCD = Fagerström Test for Cigarette Dependence; HADS = Hospital Anxiety and Depression Scale; NPSAE = neuropsychiatric adverse event; NRT =

nicotine replacement therapy (transdermal nicotine patch); PC = psychiatric cohort; SB = suicidal behavior; SE = standard error; SI = suicidal ideation.

*Categorization of FTCD into three categories was significant through its interaction with treatment, (*P*=0.04).

†Denotes a negative value near zero.

‡The main effect of the psychiatric cohort diagnosis was not significant (*P*=0.99), and estimates for pairwise comparisons have no predictive value and are not shown.

§The aggression score was the only covariate with a non-linear relationship with NPSAE. A quadratic relationship between aggression score and NPSAE is significant; the quadratic fit indicates an increasing probability of NPSAE, which maximizes at a score of 58 and then turns downward.

A significant effect was found in the screening assessment for covariates in bold.

Table 3

Results of Stepwise Regression Analysis of Predictors of NPSAE (PC)

Covariate	**Increase in Rate of Primary NPSAE Endpoint, % (SE)**	***P*-value for Effect of Covariate**
Age (1 year increase)	−0.1 (0.0)	0.002
	Or 1.0% decrease per 10.8 years increase in age	
Sex (male vs female)	−1.9 (0.6)	0.004
Prior bupropion use (yes vs no)	4.0 (1.4)	0.004
Prior NRT use (yes vs no)	1.9 (0.8)	0.012
Alcohol/substance use disorder history (yes vs no)	2.4 (0.1)	0.014
HADS anxiety total (1 unit increase)	0.3 (0.1)	0.003
	Or 1.0% increase per 3.9 units increase in HADS anxiety total	
Prior SI/SB [C-SSRS] (yes vs no)	4.4 (0.9)	0.0001

C-SSRS = Columbia-Suicide Severity Rating Scale; HADS = Hospital Anxiety and Depression Scale; NPSAE = neuropsychiatric adverse event; NRT = nicotine replacement therapy (transdermal nicotine patch); PC = psychiatric cohort; SB = suicidal behavior; SE = standard error; SI = suicidal ideation.

Table 4

Regression Results of Screening Assessment of Predictors of NPSAE (NPC)

Covariate	**Increase in Rate of Primary NPSAE Endpoint, % (SE)**	***P*-value for Effect of Covariate**	***P*-value for Treatment-by-Covariate Interaction**
Age (1 year increase)	0.0 (0.0)	0.48	0.54
Sex (male vs female)	0.2 (0.4)	0.64	0.62
Race*			0.74
White vs Black	**3.4 (0.8)**	**<0.0001**	–
Other vs Black	3.1 (1.3)	0.02	–
BMI (1 unit increase)	−0.0 (0.0)	0.52	1.00
FTCD (1 unit increase)[†]	0.1 (0.1)	0.30	0.95
Age of starting smoking (1 year increase)	−0.0 (0.0)	0.27	0.78
Prior varenicline use (yes vs no)	−0.2 (0.7)	0.77	0.52
Prior bupropion use (yes vs no)	2.0 (1.1)	0.06	0.58
Prior NRT use (yes vs no)	1.0 (0.6)	0.10	0.09
Alcohol/substance use disorder history (yes vs no)	*Too few subjects (n=8)*		
HADS anxiety total (1 point increase)	**0.3 (0.1)**	**0.0006**	0.09
	Or 1.0% increase per 2.9 units		

	increase in HADS anxiety total		
HADS depression total (1 point increase)	0.1 (0.1)	0.28	0.14
Prior SI/SB [C-SSRS] (yes vs no)	**4.8 (1.8)**	**0.008**	0.38
Aggression score [BPAQ] (1 unit increase)	0.0 (0.0)	0.87	0.26
Baseline psychotropic medication including sleeping aids (yes vs no)	0.5 (0.9)	0.58	0.09

BMI, body mass index; BPAQ, Buss-Perry Aggression Questionnaire; C-SSRS, Columbia-Suicide Severity Rating Scale; FTCD, Fagerström Test for Cigarette Dependence; HADS, Hospital Anxiety and Depression Scale; NPC, non-psychiatric cohort; NPSAE, neuropsychiatric adverse event; NRT, nicotine replacement therapy (transdermal nicotine patch); SB = suicidal behavior; SE = standard error; SI = suicidal ideation.

*Only two NPSAEs in Blacks.

†Categorization into three groups was not significant, *P*=0.68.

A significant effect was found in the screening assessment for covariates in bold.

Table 5

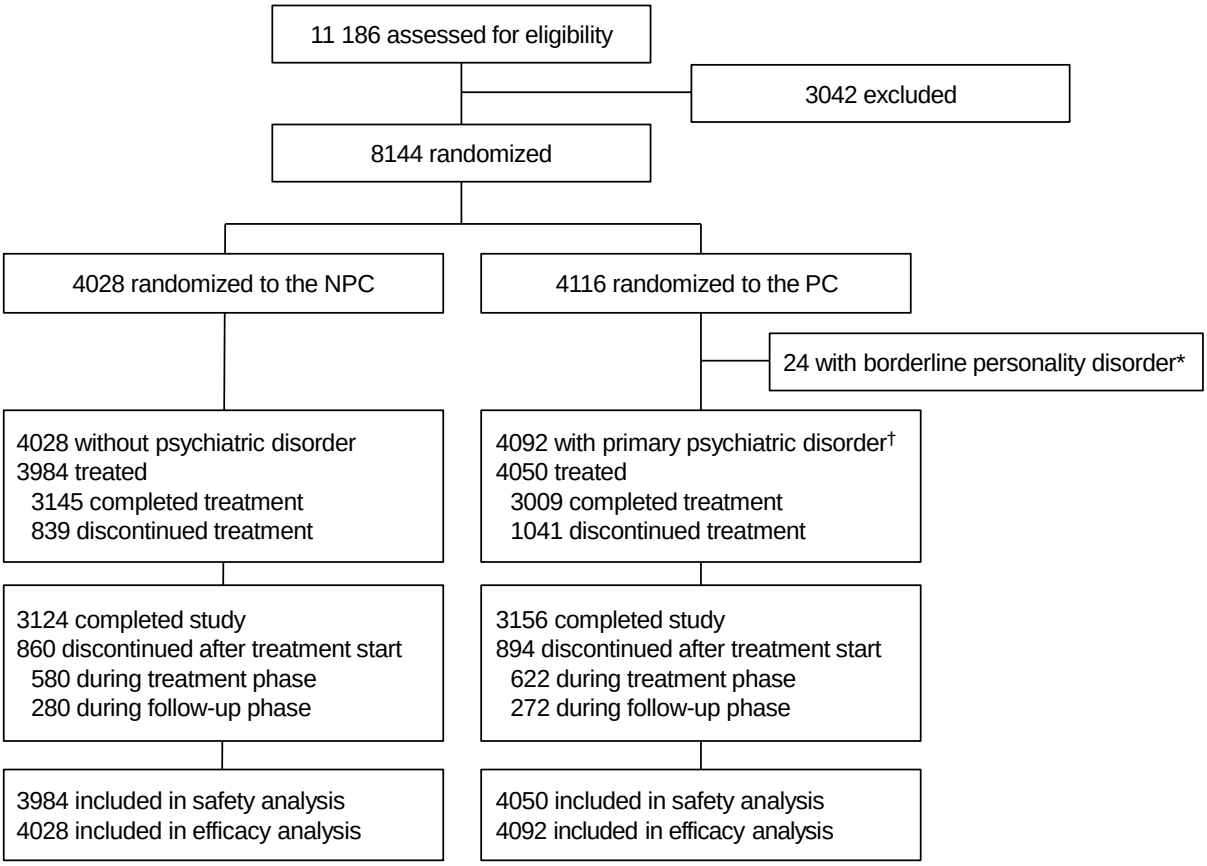
Results of Stepwise Regression Analysis of Predictors of NPSAE (NPC)

Covariate	**Increase in Rate of Primary NPSAE Endpoint, % (SE)**	***P*-value for Effect of Covariate**
Race		
White vs Black	2.5 (0.8)	0.003
Other vs Black	1.3 (1.5)	0.39
HADS anxiety total (1 point increase)	0.3 (0.1)	0.017
	Or 1.0% increase per 4.0 units increase in HADS anxiety total score	
Prior SI/SB [C-SSRS] (yes vs no)	4.1 (1.8)	0.024

C-SSRS = Columbia-Suicide Severity Rating Scale; HADS = Hospital Anxiety and Depression Scale; NPC = non-psychiatric cohort; NPSAE = neuropsychiatric adverse event; SB = suicidal behavior; SE = standard error; SI = suicidal ideation.

[[Figures]]

Figure 1.



*Excluded from the present analysis because the small size of this group did not permit accurate modeling involving this disorder
†Primary diagnosis of mood, anxiety, or psychotic disorder