



Original Investigation | Substance Use and Addiction

Assessment of Racial Differences in Pharmacotherapy Efficacy for Smoking Cessation

Secondary Analysis of the EAGLES Randomized Clinical Trial

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Abstract

IMPORTANCE Understanding Black vs White differences in pharmacotherapy efficacy and the underlying reasons is critically important to reducing tobacco-related health disparities.

OBJECTIVE To compare pharmacotherapy efficacy and examine variables to explain Black vs White differences in smoking abstinence.

DESIGN, SETTING, AND PARTICIPANTS This study is a secondary analysis of the Evaluating Adverse Events in a Global Smoking Cessation Study (EAGLES) double-blind, placebo-controlled, randomized clinical trial, which took place at clinical trial centers, academic centers, and outpatient clinics in 29 states in the US. US Black and White smokers who smoked 10 or more cigarettes per day with and without psychiatric comorbidity were enrolled between November 2011 and January 2015. Data analysis was performed from July 2019 to January 2020.

INTERVENTIONS Participants were randomized (1:1:1:1) in a double-blind, triple-dummy, placebo- and active-controlled (nicotine patch) trial of varenicline and bupropion for 12 weeks with follow-up through week 24.

MAIN OUTCOMES AND MEASURES Biochemically verified continuous cigarette abstinence rate (CAR) from weeks 9 to 24. Baseline, postbaseline treatment, and safety characteristics were examined as variables to explain race differences in abstinence.

RESULTS Of the 1065 Black smokers enrolled, 255 were randomized to receive varenicline, 259 received bupropion, 286 received nicotine replacement therapy (NRT [ie, nicotine patch]), and 265 received placebo. Among the 3044 White smokers enrolled, 778 were randomized to receive varenicline, 769 received bupropion, 738 received NRT, and 759 received placebo. Participants were predominantly female (614 Black [57.7%] and 1786 White [58.7%] women) and heavy smokers (mean [SD] cigarettes per day, 18.2 [7.9] for Black and 20.0 [7.5] for White smokers), with a mean (SD) age of 47.2 (11.2) years for Black and 46.5 (12.7) years for White participants. Treatment and race were associated with CAR for weeks 9 to 24. The CAR was 4.9% lower for Black vs White participants (odds ratio [OR], 0.53; 95% CI, 0.41-0.69; $P < .001$); differences were found across all treatments. Pooling psychiatric and nonpsychiatric cohorts, varenicline (OR, 2.63; 95% CI, 1.90-3.63; $P < .001$), bupropion (OR, 1.75; 95% CI, 1.25-2.46; $P = .001$), and NRT (OR, 1.52; 95% CI, 1.07-2.16; $P = .02$) had greater efficacy than placebo for White participants. Only varenicline (OR, 2.63; 95% CI, 1.26-5.48; $P = .01$) had greater efficacy than placebo for Black participants. Baseline, postbaseline, and safety characteristics differed by race, but these variables did not eliminate the association of race with CAR. Black participants had 49% reduced odds of CAR for weeks 9 to 24 compared with White participants in the adjusted model (OR, 0.51; 95% CI, 0.39-0.66; $P < .001$).

(continued)

Key Points

Question Does the efficacy of varenicline, bupropion, and nicotine patch differ for US Black and White smokers, and what variables explain the difference?

Findings In this secondary analysis of US participants in the EAGLES randomized clinical trial, Black smokers were less likely than White smokers to quit. All treatments had greater efficacy than placebo for White smokers, but only varenicline had greater efficacy than placebo for Black smokers; baseline, postbaseline, and safety characteristics did not explain the race difference in abstinence.

Meaning Understanding variables (eg, socioeconomic, biological) beyond those explored that underlie Black vs White differences in pharmacotherapy efficacy may improve treatment outcomes.

+ Supplemental content

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Abstract (continued)

CONCLUSIONS AND RELEVANCE Black and White smokers achieved the highest rate of abstinence while taking varenicline, suggesting that it is the best first-line therapy for these groups. However, Black smokers were less responsive to all therapies, including placebo. Understanding variables (eg, socioeconomic or biological) beyond those may lead to improved treatment outcomes for Black smokers.

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Introduction

Tobacco remains the leading cause of preventable morbidity and mortality in the US, accounting for more than 480 000 total deaths and more than 34% of all cancer deaths annually.¹ Although non-Hispanic Black individuals (referred to hereafter as Black) have a prevalence of smoking that is comparable to that of non-Hispanic White individuals (referred to hereafter as White), smoke fewer cigarettes per day (CPD), and smoke on fewer days of the month,²⁻⁵ they have higher rates of smoking-related morbidity and mortality.⁶⁻⁸

Racial/ethnic differences in quitting are not well understood.⁹ Cross-sectional and cohort studies^{3,10-17} consistently find that Black smokers are less likely than White smokers to quit despite Black smokers making more quit attempts. The results of randomized clinical trials (RCTs) have been more mixed, with approximately half finding no difference in cessation rates between Black and White smokers,¹⁸⁻²⁴ half finding higher cessation rates among White smokers,²⁵⁻³³ and only 1 finding higher cessation rates among Black smokers.³⁴ None of these RCTs examined variables to explain the race difference, leaving unanswered questions about why Black smokers experience lower cessation rates compared with White smokers. Secondary analyses of Evaluating Adverse Events in a Global Smoking Cessation Study (EAGLES), the largest and most comprehensive smoking cessation study to date, also found that Black smokers were significantly less likely than White smokers to quit across all treatments, including varenicline, bupropion, nicotine replacement therapy (NRT [ie, nicotine patch]), and placebo, but did not explore reasons to explain the race difference in abstinence.³³

Elucidating variables that explain racial/ethnic differences in abstinence is critically important to reducing tobacco-related health disparities.⁵ Most studies examine barriers and facilitators to abstinence in Black and White smokers separately.³⁵⁻⁴⁰ This contributes to knowledge about the variables associated with quitting for Black smokers and for White smokers, including variables such as CPD, nicotine dependence, and nicotine metabolism,^{11,18,41-53} but does little to explain why Black vs White differences in abstinence exist. A recent study by Nollen et al,³¹ prospectively designed to examine this question, found that Black smokers achieved lower quit rates than White smokers when provided the same treatment of varenicline in combination with smoking cessation counseling.³¹ Preplanned secondary analyses demonstrated that the difference in abstinence was not associated with race or biological differences in nicotine metabolism, but rather was explained by socioeconomic factors, treatment process, and smoking characteristics. A better understanding of variables associated with race that make it harder for Black smokers in the US to quit smoking compared with White smokers is needed to reduce tobacco-related health disparities.

EAGLES was a large, multicenter, placebo-controlled RCT examining the safety and efficacy of varenicline, bupropion, and NRT for smoking cessation.²⁵ The size, design, and number of Black and White smokers enrolled provide an opportunity to assess variables to explain race-related differences in quitting. The present article reports post hoc secondary analyses that (1) compare the efficacy of varenicline, bupropion, NRT, and placebo between and within US Black and White

smokers; and (2) examine baseline, postbaseline, and safety characteristics associated with race to explain the Black vs White difference in abstinence.

Methods

Design

EAGLES was a randomized (1:1:1), double-blind, triple-dummy, placebo-controlled and active-controlled (NRT; 21 mg per day with taper) trial of varenicline (1 mg twice daily) and bupropion (150 mg twice daily) for 12 weeks with 12-week nontreatment follow-up. The published trial report provides full details of study design and outcomes.²⁵ The trial protocol is available in [Supplement 1](#). Reporting follows the Consolidated Standards of Reporting Trials ([CONSORT](#)) reporting guideline for randomized studies. Written consent forms and study procedures were approved by the institutional review boards or ethics committees at participating institutions.

Participants

Participants in EAGLES were 8144 male and female smokers, aged 18 to 75 years, with and without prespecified current or lifetime psychiatric diagnoses, who smoked 10 or more CPD. They were recruited from 16 countries, including the US, between November 2011 and January 2015. A list of participating study sites was previously published.²⁵ The sample included smokers meeting diagnostic criteria for psychotic, anxiety, mood, and borderline personality disorders per structured clinical interview, with stable treatment and no imminent risk of self-harm.⁵⁴

Most EAGLES participants (95.9%) were either White or Black. Race was self-identified by the participant. Yet with 52.3% of participants enrolled in the US, there was a race imbalance for US vs non-US participants (US, 71.5% White vs 25.0% Black participants; non-US, 92.8% White vs 2.5% Black participants). To avoid potential confounding issues, the current analyses restricted inclusion to US White or Black participants. The sample was not powered, a priori, to detect differences in efficacy associated with race and possible interactions with treatment group or cohort.

Measures

Outcomes

As per the Russell Standard, the continuous cigarette abstinence rate (CAR) for weeks 9 to 24 was used as the primary end point here because longer periods of abstinence are more strongly associated with lifetime abstinence.⁵⁵ The CAR for weeks 9 to 12 and 7-day point prevalence abstinence (PPA) each week from weeks 0 to 24 were also explored. Participants were considered abstinent if they self-reported cigarette abstinence throughout the specified period in conjunction with exhaled carbon monoxide concentration less than 10 ppm. Missing self-reported data were classified as smokers.⁵⁵

Variables Explored

Demographic characteristics included sex, age, and body mass index (calculated as weight in kilograms divided by height in meters squared). Smoking characteristics included CPD in the month prior to enrollment, cigarette dependence (Fagerström Test for Cigarette Dependence),⁵⁶ age of starting smoking, length of time as smoker, and lifetime serious quit attempts (yes or no and number). Treatment process characteristics included prior use of varenicline, bupropion, or NRT (none vs any) and history of suicidal ideation and/or behavior (none vs any), captured through the Columbia-Suicide Severity Rating Scale.⁵⁷ Psychosocial characteristics included history of a psychiatric diagnosis (defined as the primary diagnosis: none, mood disorder, anxiety disorder, psychotic disorder, or borderline personality disorder), alcohol or substance abuse disorder via structured clinical interview,⁵⁴ anxiety score (Hospital Anxiety and Depression Scale),⁵⁸ depression score (Hospital Anxiety and Depression Scale),⁵⁸ aggression score (Buss-Perry Aggression Questionnaire),⁵⁹ and use of psychotropic medication, including sleep aids (none vs any).

Postbaseline characteristics included discontinuation from the study, discontinuation from the study drug, lost to follow-up, days' exposure to study drug, treatment compliance (80% or 68-day threshold), change in anxiety and depression during the treatment period, treatment-emergent composite neuropsychiatric end point, and mild, moderate, or severe adverse events (AEs). Measurement and computation of postbaseline characteristics have been defined in detail in Anthenelli et al²⁵ and are included in eTable 1 in [Supplement 2](#).

Statistical Analysis

Statistical analyses were performed using SAS statistical software version 9.4 (SAS Institute). Tests and 95% CIs are 2-sided and use a 5% level of significance (eg, stepwise regression entry and stay thresholds were $P < .05$) except for candidate covariate assessment, which invoked a nominal $P < .10$ rule.

For weeks 9 to 24 (and separately for weeks 9 to 12), the CAR was analyzed via logistic regression with a fully crossed model of treatment group, psychiatric cohort, and race to produce odds ratio (OR) and 95% CI summaries. An analogous general linear model (with identity link) yielded risk difference (RD) and 95% CI summaries.

Covariate inclusion was a multistep process, where first a simple χ^2 test (categorical case) or t test (numerical case) compared a potential variable (1) across race and (2) across cigarette abstinence. Variables that differed by both race and abstinence ($P < .10$ for each) were candidate variables for inclusion in the subsequent stepwise logistic regression analysis, as was race and each race-by-candidate interaction. Treatment and cohort were forced inclusion terms as study design factors. The identified pool of candidate variables was assessed in a stepwise fashion. Stepwise logistic regression was performed separately for baseline variables and for postbaseline variables (the latter being anecdotal in nature). Finally, for each cigarette abstinence end point, the included covariates from these 2 models became candidates in another stepwise logistic regression.

Seven-day PPA and CPD among continuing smokers were examined for Black and White participants in a descriptive fashion by treatment and psychiatric cohort. The presented analyses were performed July 2019 to January 2020, were not preplanned, and should be considered exploratory.

Results

Participant Characteristics

This study included 1065 US Black participants (255 receiving varenicline, 259 receiving bupropion, 286 receiving NRT, and 265 receiving placebo) and 3044 US White participants (778 receiving varenicline, 769 receiving bupropion, 738 receiving NRT, and 759 receiving placebo) with and without psychiatric disorders (**Figure 1**). Characteristics of the sample are shown in eTable 1 in [Supplement 2](#). Participants were predominantly female (614 Black [57.7%] and 1786 White [58.7%] women) and heavy smokers (mean [SD] CPD, 18.2 [7.9] for Black participants and 20.0 [7.5] for White participants), with a mean (SD) age of 47.2 (11.2) years for Black participants and 46.5 (12.7) years for White participants.

Cigarette Abstinence

Only treatment and race were associated with CAR for weeks 9 to 24 (eTable 2 in [Supplement 2](#)). The CAR for weeks 9 to 24 was 12.5% (382 of 3044) for White participants and 7.0% (75 of 1065) for Black participants. The absolute difference in CAR for weeks 9 to 24 was 4.9% less for Black participants compared with White participants (OR, 0.53; 95% CI, 0.41-0.69; $P < .001$) (eTable 3 in [Supplement 2](#)). **Figure 2** illustrates CAR for weeks 9 to 24 for race by treatment and cohort. Pooling psychiatric cohorts, the CAR for weeks 9 to 24 for Black participants compared with White participants was 10.3% vs 18.1% for varenicline (OR, 0.52; 95% CI, 0.33-0.82, $P = .004$), 5.8% vs 12.9% for bupropion (OR, 0.42; 95% CI, 0.24-0.74, $P = .003$), 7.9% vs 11.4% for NRT (OR, 0.67; 95%

CI, 0.41-1.09, $P = .11$), and 4.2% vs 7.8% for placebo (OR, 0.52; 95% CI, 0.27-1.01; $P = .05$). For the psychiatric cohort only, the ORs for Black participants compared with White participants were 0.40 (95% CI, 0.20-0.79; $P = .009$) for varenicline, 0.40 (95% CI, 0.19-0.83; $P = .01$) for bupropion, 0.53 (95% CI, 0.26-1.05; $P = .07$) for NRT, and 0.48 (95% CI, 0.20-1.17; $P = .11$) for placebo. For the nonpsychiatric cohort only, the ORs for Black participants compared with White participants were 0.68 (95% CI, 0.38-1.21; $P = .19$) for varenicline, 0.44 (95% CI, 0.18-1.07; $P = .07$) for bupropion, 0.84 (95% CI, 0.42-1.71; $P = .64$) for NRT, and 0.56 (95% CI, 0.21-1.50; $P = .25$) for placebo.

Figure 1. CONSORT Flow Diagram

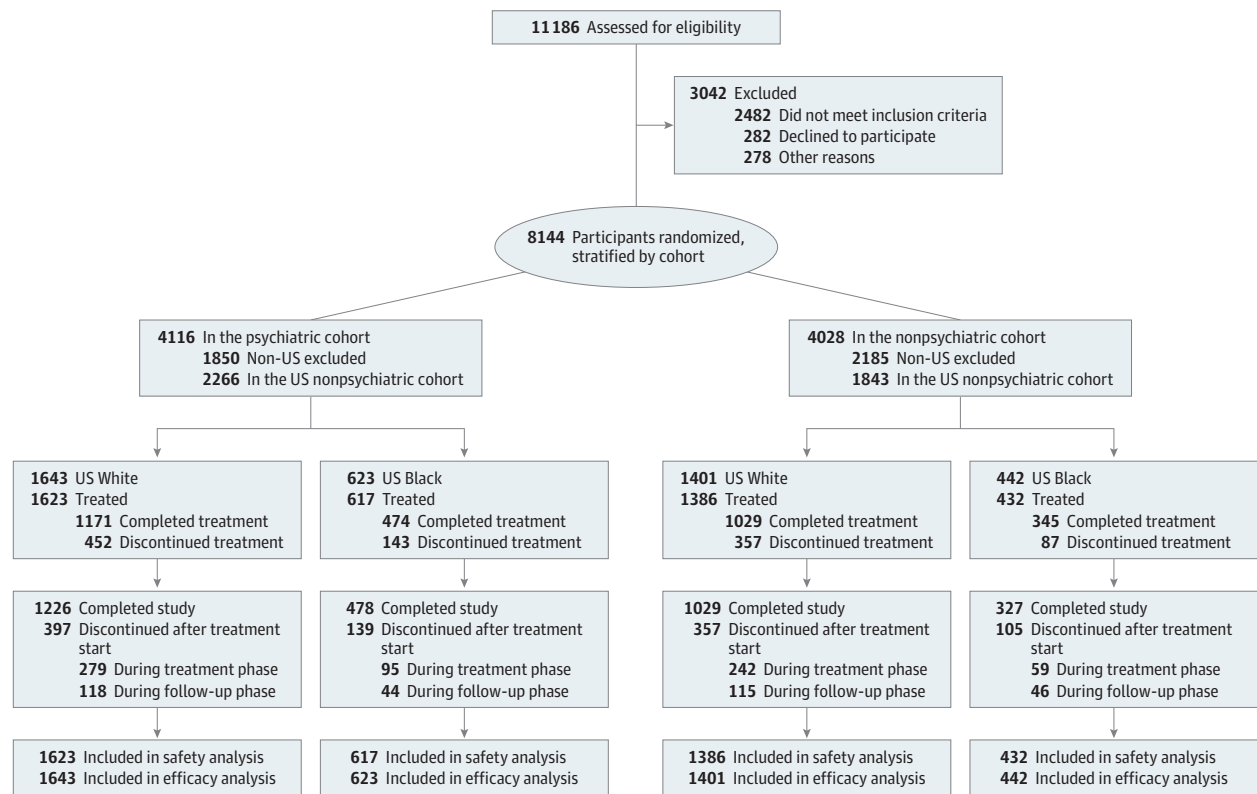
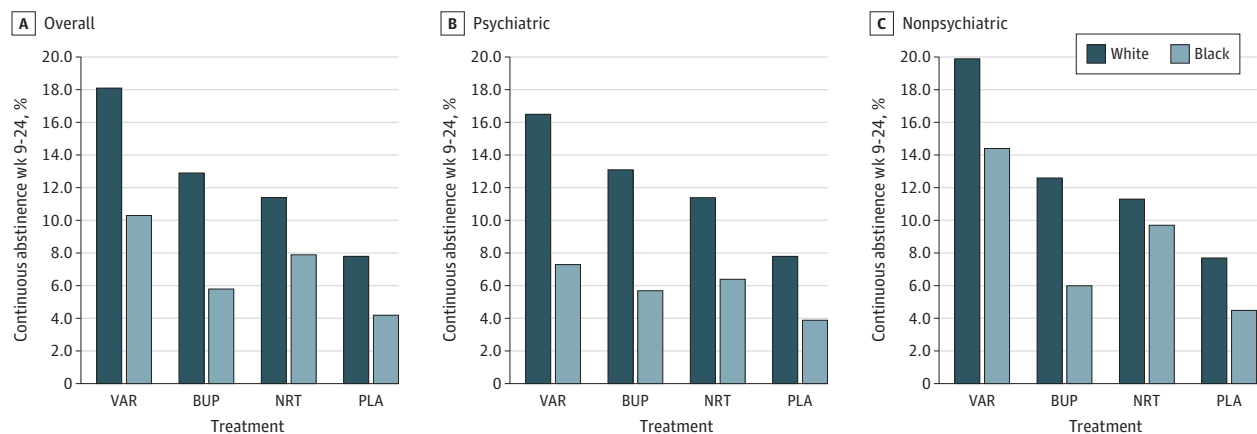


Figure 2. Continuous Cigarette Abstinence Rates for Weeks 9 to 24 for Black and White Smokers by Treatment, Cohort, and Overall



BUP indicates bupropion; NRT, nicotine replacement therapy; PLA, placebo; and VAR, varenicline.

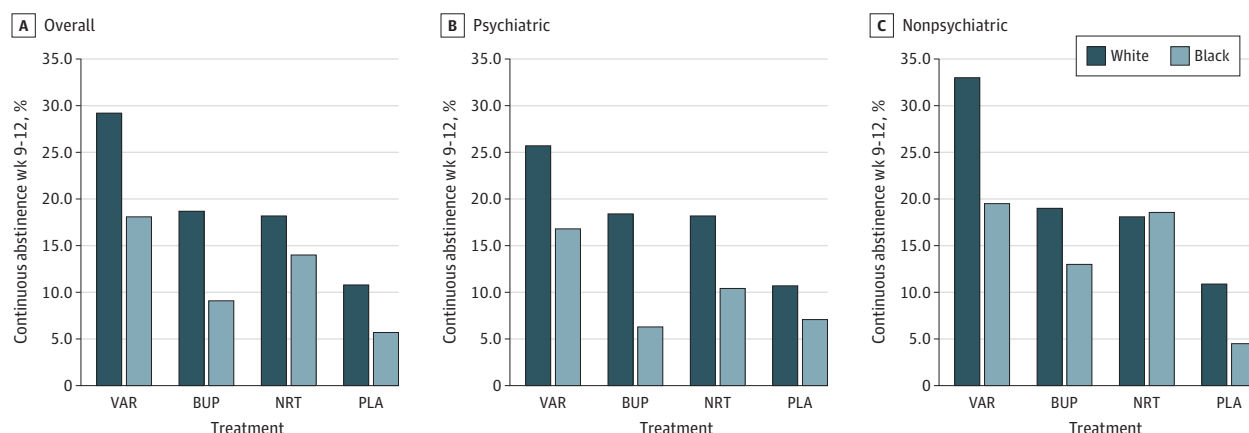
Similarly, the CAR for weeks 9 to 12 was 19.2% (585 of 3044) for White participants and 11.6% (124 of 1065) for Black participants. The absolute difference in CAR for weeks 9 to 12 was 6.6% less for Black participants compared with White participants (OR, 0.56; 95% CI, 0.45-0.69; $P < .001$) (eTable 3 in Supplement 2). At the end of treatment, cohort was also associated with CAR for weeks 9 to 12. **Figure 3** presents abstinence by cohort. For the pooled cohorts, the ORs for Black participants compared with White participants were 0.54 (95% CI, 0.38-0.76; $P < .001$) for varenicline, 0.43 (95% CI, 0.27-0.69; $P < .001$) for bupropion, 0.73 (95% CI, 0.50-1.08; $P = .12$) for NRT, and 0.50 (95% CI, 0.28-0.90; $P = .02$) for placebo. For the psychiatric cohort only, the ORs for Black participants compared with White participants were 0.58 (95% CI, 0.36-0.96; $P = .03$) for varenicline, 0.30 (95% CI, 0.15-0.59; $P < .001$) for bupropion, 0.52 (95% CI, 0.30-0.91; $P = .02$) for NRT, and 0.64 (95% CI, 0.32-1.27; $P = .20$) for placebo. For the nonpsychiatric cohort only, the ORs for Black participants compared with White participants were 0.49 (95% CI, 0.30-0.82; $P = .006$) for varenicline, 0.64 (95% CI, 0.33-1.20; $P = .16$) for bupropion, 1.03 (95% CI, 0.60-1.78; $P = .91$) for NRT, and 0.39 (95% CI, 0.15-1.01; $P = .05$) for placebo.

Comparison of the relative efficacy of treatments within race is shown in **Table 1**. Among White participants and pooling psychiatric cohorts, varenicline resulted in significantly higher odds of CAR for weeks 9 to 24 than bupropion (OR, 1.50; 95% CI, 1.14-1.99; $P = .004$), NRT (OR, 1.73; 95% CI, 1.29-2.31; $P < .001$), and placebo (OR, 2.63; 95% CI, 1.90-3.63; $P < .001$); compared with placebo, bupropion (OR, 1.75; 95% CI, 1.25-2.46; $P = .001$) and NRT (OR, 1.52; 95% CI, 1.07-2.16; $P = .02$) resulted in significantly higher odds of quitting. The relative efficacy of bupropion vs NRT did not differ for White participants (OR, 1.15; 95% CI, 0.84-1.57; $P = .38$). Among Black participants and pooling across psychiatric cohorts, varenicline resulted in significantly higher odds of CAR for weeks 9 to 24 than placebo (OR, 2.63; 95% CI, 1.26-5.48; $P = .01$), but no significant differences were seen in the relative efficacy of varenicline vs bupropion or NRT, bupropion and NRT vs placebo, and bupropion vs NRT.

Differences in Baseline and Postbaseline Variables by Race and CAR

Baseline age, heaviness of smoking, cigarette dependence, age of smoking initiation, lifetime (serious) quit attempts, psychiatric diagnosis, aggression, anxiety, and depression scores differed between Black participants and White participants and were also associated with CAR for weeks 9 to 24 (eTable 1 in Supplement 2). Postbaseline differences demonstrated that Black participants were less likely to be discontinued from the study drug, had greater study drug compliance overall and days of exposure to the study drug, greater reduction in depression, and fewer psychiatric and

Figure 3. Continuous Cigarette Abstinence Rates for Weeks 9 to 12 for Black and White Smokers by Treatment, Cohort, and Overall



BUP indicates bupropion; NRT, nicotine replacement therapy; PLA, placebo; and VAR, varenicline.

Table 1. Comparison of the Relative Efficacy of Treatments via RDs and ORs for White and Black Smokers Overall and by Psychiatric Cohort

Variable	Overall		Psychiatric cohort		Nonpsychiatric cohort	
	White smokers	Black smokers	White smokers	Black smokers	White smokers	Black smokers
CAR wk 9-24						
VAR vs BUP						
RD, % (95% CI)	5.3 (1.7 to 9.0)	5.0 (0.2 to 9.9)	3.4 (-1.4 to 8.2)	1.6 (-4.0 to 7.3)	7.3 (1.8 to 12.7)	8.4 (0.5 to 16.3)
<i>p</i> ^a	.004	.04	.16	.57	.009	.04
OR (95% CI)	1.50 (1.14 to 1.99)	1.86 (0.95 to 3.65)	1.31 (0.90 to 1.92)	1.31 (0.52 to 3.33)	1.72 (1.14 to 2.59)	2.64 (1.00 to 6.97)
<i>p</i> ^b	.004	.07	.16	.57	.009	.05
VAR vs NRT						
RD, % (95% CI)	6.8 (3.2 to 10.4)	2.8 (-2.2 to 7.9)	5.1 (0.4 to 9.8)	0.9 (-4.7 to 6.6)	8.6 (3.2 to 13.9)	4.7 (-3.7 to 13.0)
<i>p</i> ^a	<.001	.28	.04	.75	.002	.27
OR (95% CI)	1.73 (1.29 to 2.31)	1.35 (0.74 to 2.45)	1.53 (1.02 to 2.29)	1.16 (0.48 to 2.82)	1.94 (1.27 to 2.96)	1.56 (0.70 to 3.50)
<i>p</i> ^b	<.001	.33	.04	.74	.002	.28
VAR vs PLA						
RD, % (95% CI)	10.4 (7.1 to 13.8)	6.7 (2.1 to 11.2)	8.7 (4.4 to 13.1)	3.4 (-1.9 to 8.7)	12.1 (7.1 to 17.2)	9.9 (2.5 to 17.3)
<i>p</i> ^a	<.001	.004	<.001	.21	<.001	.009
OR (95% CI)	2.63 (1.90 to 3.63)	2.63 (1.26 to 5.48)	2.34 (1.50 to 3.63)	1.94 (0.69 to 5.49)	2.96 (1.84 to 4.75)	3.57 (1.27 to 10.0)
<i>p</i> ^b	<.001	.01	<.001	.21	<.001	.02
BUP vs NRT						
RD, % (95% CI)	1.5 (-1.8 to 4.8)	-2.2 (-6.6 to 2.2)	1.7 (-2.9 to 6.2)	-0.7 (-5.8 to 4.4)	1.3 (-3.5 to 6.0)	-3.7 (-10.9 to 3.4)
<i>p</i> ^a	.38	.32	.47	.79	.60	.31
OR (95% CI)	1.15 (0.84 to 1.57)	0.72 (0.36 to 1.44)	1.17 (0.76 to 1.79)	0.88 (0.36 to 2.19)	1.13 (0.72 to 1.78)	0.59 (0.21 to 1.66)
<i>p</i> ^b	.38	.36	.47	.79	.60	.32
BUP vs PLA						
RD, % (95% CI)	5.1 (2.0 to 8.1)	1.6 (-2.2 to 5.5)	5.3 (1.1 to 9.5)	1.8 (-3.0 to 6.5)	4.9 (0.4 to 9.3)	1.5 (-4.6 to 7.5)
<i>p</i> ^a	.001	.41	.01	.46	.03	.63
OR (95% CI)	1.75 (1.25 to 2.46)	1.42 (0.63 to 3.17)	1.78 (1.12 to 2.82)	1.48 (0.51 to 4.26)	1.72 (1.04 to 2.84)	1.35 (0.40 to 4.58)
<i>p</i> ^b	.001	.40	.01	.47	.03	.63
NRT vs PLA						
RD, % (95% CI)	3.6 (0.6 to 6.6)	3.8 (-0.3 to 7.9)	3.6 (-0.5 to 7.7)	2.5 (-2.3 to 7.2)	3.6 (-0.7 to 7.9)	5.2 (-1.5 to 11.9)
<i>p</i> ^a	.02	.07	.08	.31	.10	.13
OR (95% CI)	1.52 (1.07 to 2.16)	1.96 (0.93 to 4.13)	1.52 (0.94 to 2.46)	1.67 (0.60 to 4.64)	1.52 (0.91 to 2.54)	2.29 (0.77 to 6.81)
<i>p</i> ^b	.02	.08	.08	.32	.11	.14
CAR wk 9-12						
VAR vs BUP						
RD, % (95% CI)	10.6 (6.4 to 14.9)	8.5 (2.4 to 14.6)	7.2 (1.7 to 12.8)	10.5 (3.2 to 17.8)	14.0 (7.6 to 20.4)	6.5 (-3.2 to 16.2)
<i>p</i> ^a	<.001	.006	.01	.005	<.001	.19
OR (95% CI)	1.79 (1.41 to 2.27)	2.21 (1.29 to 3.78)	1.53 (1.10 to 2.12)	3.01 (1.38 to 6.57)	2.10 (1.48 to 2.97)	1.62 (0.77 to 3.39)
<i>p</i> ^b	<.001	.004	.01	.006	<.001	.20
VAR vs NRT						
RD, % (95% CI)	11.2 (6.9 to 15.5)	3.6 (-2.7 to 10.0)	7.5 (1.9 to 13.1)	6.4 (-1.4 to 14.1)	14.9 (8.5 to 21.3)	0.9 (-9.2 to 11.0)
<i>p</i> ^a	<.001	.26	.009	.11	<.001	.86
OR (95% CI)	1.86 (1.46 to 2.38)	1.36 (0.85 to 2.16)	1.56 (1.11 to 2.18)	1.74 (0.90 to 3.37)	2.23 (1.57 to 3.17)	1.06 (0.55 to 2.05)
<i>p</i> ^b	<.001	.20	.01	.10	<.001	.86
VAR vs PLA						
RD, % (95% CI)	18.6 (14.6 to 22.5)	12.3 (6.8 to 17.8)	15.0 (9.9 to 20.0)	9.6 (2.2 to 17.1)	22.2 (16.2 to 28.1)	15.0 (6.9 to 23.1)
<i>p</i> ^a	<.001	<.001	<.001	.01	<.001	<.001
OR (95% CI)	3.41 (2.58 to 4.50)	3.67 (1.95 to 6.89)	2.88 (1.97 to 4.20)	2.62 (1.23 to 5.61)	4.04 (2.69 to 6.06)	5.13 (1.88 to 14.0)
<i>p</i> ^b	<.001	<.001	<.001	.01	<.001	.001
BUP vs NRT						
RD, % (95% CI)	0.6 (-3.3 to 4.5)	-4.8 (-10.5 to 0.8)	0.3 (-5.1 to 5.6)	-4.1 (-10.0 to 1.8)	0.9 (-4.8 to 6.6)	-5.6 (-15.3 to 4.2)
<i>p</i> ^a	.77	.10	.92	.17	.75	.26
OR (95% CI)	1.04 (0.80 to 1.35)	0.62 (0.35 to 1.07)	1.02 (0.71 to 1.46)	0.58 (0.26 to 1.29)	1.06 (0.73 to 1.55)	0.65 (0.31 to 1.39)
<i>p</i> ^b	.77	.08	.92	.18	.75	.27

(continued)

Table 1. Comparison of the Relative Efficacy of Treatments via RDs and ORs for White and Black Smokers Overall and by Psychiatric Cohort (continued)

Variable	Overall		Psychiatric cohort		Nonpsychiatric cohort	
	White smokers	Black smokers	White smokers	Black smokers	White smokers	Black smokers
BUP vs PLA						
RD, % (95% CI)	7.9 (4.4 to 11.5)	3.8 (-0.9 to 8.5)	7.7 (2.9 to 12.5)	-0.9 (-6.4 to 4.7)	8.2 (2.9 to 13.4)	8.5 (0.9 to 16.1)
<i>P</i> ^a	<.001	.11	.002	.76	.002	.03
OR (95% CI)	1.90 (1.42 to 2.55)	1.66 (0.83 to 3.33)	1.88 (1.26 to 2.81)	0.87 (0.36 to 2.12)	1.93 (1.26 to 2.95)	3.17 (1.09 to 9.23)
<i>P</i> ^b	<.001	.15	.002	.76	.003	.04
NRT vs PLA						
RD, % (95% CI)	7.3 (3.8 to 10.9)	8.7 (3.6 to 13.8)	7.5 (2.6 to 12.3)	3.3 (-2.8 to 9.4)	7.2 (2.1 to 12.4)	14.1 (5.9 to 22.2)
<i>P</i> ^a	<.001	<.001	.003	.30	.006	<.001
OR (95% CI)	1.83 (1.36 to 2.46)	2.70 (1.42 to 5.13)	1.85 (1.23 to 2.77)	1.51 (0.69 to 3.31)	1.81 (1.18 to 2.79)	4.84 (1.75 to 13.3)
<i>P</i> ^b	<.001	.002	.003	.30	.007	.002

Abbreviations: BUP, bupropion; CAR, continuous cigarette abstinence rate; NRT, nicotine replacement therapy (transdermal nicotine patch); OR, odds ratio; PLA, placebo; RD, risk difference; VAR, varenicline.

^a *P* value for RD.

^b *P* value for OR.

Table 2. Final Stepwise Logistic Regression Modeling of Continuous Cigarette Abstinence Rates for Weeks 9 to 24 With Baseline and Postbaseline Factors^a

Factors	OR (95% CI)	<i>P</i> value
Discontinued from study drug		
No	[Reference]	
Yes	0.27 (0.19-0.37)	<.001
Cigarette dependence (Fagerström Test for Cigarette Dependence)	0.91 (0.86-0.97)	<.001
Race		
White	[Reference]	
Black	0.51 (0.39-0.66)	<.001
Change in depression (HADS)	0.89 (0.85-0.93)	<.001
Age	1.02 (1.01-1.03)	<.001
Cigarettes per day in the past month	0.97 (0.95-0.99)	<.001
Anxiety (HADS)	0.94 (0.90-0.97)	<.001
Lifetime quit attempts		
No	[Reference]	
Yes	1.77 (1.20-2.62)	.002
No. of mild, moderate, or severe treatment-emergent adverse events	1.03 (1.00-1.06)	.02

Abbreviations: HADS, Hospital Anxiety and Depression Scale; OR, odds ratio.

^a Baseline and postbaseline factors associated with race and abstinence at *P* < .10 were modeled jointly. The main effects of race, each factor, and the race by factor interaction subsequently entered in a stepwise fashion. Only factors associated with abstinence at *P* < .05 were retained in the final model. The model is adjusted for treatment group and cohort (psychiatric, nonpsychiatric), which were entered and retained in the model because they were inherent in the study design.

nonpsychiatric AEs over the study period (eTable 1 in Supplement 2). Of these postbaseline variables, all but neuropsychiatric AEs were also associated with CAR for weeks 9 to 24.

Variables Associated With CAR

Results of the baseline and postbaseline variables, modeled separately, are shown in eTable 4 in Supplement 2. Results of the final stepwise logistic regression of baseline and postbaseline variables that together modeled CAR for weeks 9 to 24 are shown in Table 2. The effect of race was not statistically eliminated from the model, with Black participants having a 49% reduced odds of abstinence compared with White participants (OR, 0.51; 95% CI, 0.39-0.66; *P* < .001). Other variables that decreased the likelihood of abstinence included discontinuation from the study drug (OR, 0.27; 95% CI, 0.19-0.37; *P* < .001), greater cigarette dependence (OR, 0.91; 95% CI, 0.86-0.97; *P* < .001), heavier smoking (OR, 0.97; 95% CI, 0.95-0.99; *P* < .001), higher baseline anxiety (OR, 0.94; 95% CI, 0.90-0.97; *P* < .001), and an increase in depression over time (OR, 0.89; 95% CI, 0.85-0.93; *P* < .001). Older age (OR, 1.02; 95% CI, 1.01-1.03; *P* < .001), lifetime quit attempts (OR, 1.77; 95% CI, 1.20-2.62; *P* = .002), and experiencing more treatment-related AEs (OR, 1.03; 95% CI, 1.00-1.06; *P* = .02) increased the likelihood of abstinence. A nearly identical pattern was found in the modeling

of CAR for weeks 9 to 12 (eTable 5, eTable 6, and eTable 7 in [Supplement 2](#)); race remained in the model, with Black participants having a 47% reduced odds of abstinence compared with White participants (OR, 0.53; 95% CI, 0.43-0.67; $P < .001$).

PPA and CPD

Because prior studies have found that PPA increases over time with varenicline,^{60,61} we explored the time course in 7-day self-reported PPA and cigarettes per day in a given week by race within treatment and cohort (eFigure 1 and eFigure 2 in [Supplement 2](#)). Seven-day PPA mirrored continuous abstinence, with generally higher rates of abstinence among White participants and the nonpsychiatric cohorts. Among the varenicline-treated group, abstinence peaked between weeks 9 and 13 and stayed the same or declined from week 13 to week 23, whereas a posttreatment benefit of NRT emerged in the Black nonpsychiatric cohort.

Discussion

This study confirmed prior Black-White differences in abstinence reported in RCTs.²⁵⁻³³ Black participants were significantly less likely to quit overall, irrespective of treatment or placebo, although differences in quit rates were somewhat greater for varenicline and bupropion at long-term follow-up than for NRT or placebo. Differences in abstinence between Black and White smokers do not appear to be a pharmacological interaction in that the same effect is seen with placebo. Differences are similar to those reported in previous studies,²⁵⁻³³ and should not be interpreted to mean that pharmacotherapies are not effective for Black smokers but rather that, on average, Black smokers have lower rates of quitting on these therapies compared with White smokers. Rates of abstinence were lower across all treatments than those reported in prior studies.^{26,29,31,43,48,62-64} Lower rates of abstinence are likely due to inclusion of a large psychiatric cohort, lower-intensity behavioral counseling, and the use of the more stringent continuous abstinence vs PPA measure.⁶⁵

All active treatments had greater efficacy than placebo for White smokers at long-term follow-up (week 24) but only varenicline had greater relative efficacy than placebo for Black smokers. To our knowledge, this is the first comparison of the relative efficacy of 3 active treatments and placebo by race in a single study, with the data indicating that varenicline appears to be the best first-line treatment for both Black and White smokers. This is consistent with previous research that suggests that varenicline is the most effective of available smoking cessation pharmacotherapies.⁶⁶

Lack of difference in the long-term relative efficacy of bupropion and NRT to placebo in Black smokers should be interpreted in light of the time frame (short or long term) and cohort (psychiatric or nonpsychiatric). Among Black smokers in the nonpsychiatric cohort, both bupropion and NRT had significantly higher relative efficacy than placebo during active treatment (weeks 9-12). Specifically, Black smokers in the nonpsychiatric cohort had 3 times the odds of quitting while taking bupropion vs placebo and nearly 5 times the odds of quitting with NRT vs placebo from weeks 9 to 12. These findings suggest that long-term pharmacotherapy (>12 weeks), particularly bupropion and NRT, may be important for Black smokers given that the effects of these therapies diminished at the end of treatment and were not significantly different from placebo at long-term follow-up. Similar relapse effects have been seen with Black smokers taking bupropion in previous trials.⁴³ Extended treatment has been found to be effective in White smokers but is understudied in Black smokers.^{60,63,67,68} Future research is needed in this area. Little is known about pharmacotherapy efficacy in Black smokers with psychiatric comorbidities. Findings from this study suggest that this group may be particularly recalcitrant to treatment and that it is an important group for future studies.

Race remained significantly associated with short- and long-term abstinence after accounting for variables that differed by race. Race differences in abstinence may be explained by variables not measured in EAGLES. The study by Nollen et al³¹ evaluated many of the same smoking, treatment, and psychosocial variables but also included comprehensive measures of socioeconomic and biological characteristics; analyses found that socioeconomic variables, namely home ownership,

income, and neighborhood disadvantage, in addition to visit attendance and cotinine levels, explained the Black-White difference in abstinence among varenicline-treated smokers. Socioeconomically disadvantaged adults are less likely to achieve abstinence,^{5,69} and Black smokers in the US are more socioeconomically disadvantaged than White smokers.^{41,47,50-52,70-80} Socioeconomic variables were not measured in EAGLES and, therefore, we cannot speculate about their impact, but results of Nollen et al³¹ and other studies^{26,33,73,81} suggest that socioeconomic variables should be considered within the context of clinical trials. Addressing the pathways linking socioeconomic status to cessation (ie, stress, coping, psychological distress) has been found to attenuate the impact of socioeconomic status on abstinence and could be particularly important for the most socioeconomically disadvantaged smokers.⁴¹

Limitations

Several limitations warrant consideration. EAGLES was not designed or powered to examine race differences in abstinence. The large sample size allowed us to detect significant effects that may lack clinical relevance. It is unlikely, however, that a smoking cessation pharmacotherapy study of the size and scope of EAGLES will be conducted any time in the future and, therefore, limitations must be considered within the context of this strength. The results are also hypothesis-generating and point to important areas of future study regarding the relative efficacy of smoking cessation pharmacotherapy for Black participants and White participants and the need to prospectively design studies to examine variables underlying Black-White differences in abstinence. In addition to socioeconomic status, other key covariates known to be associated with abstinence, including menthol,^{42,45,46,49,82} nicotine metabolism,^{48,83-86} and social and environmental contexts associated with racism, discrimination, and increased stress^{50,70-80} were not assessed and may have contributed to our inability to explain the race difference in abstinence. Information on history, treatment, or level of care for psychiatric comorbidities was not assessed in EAGLES. Black participants and continued smokers had greater likelihood of a psychiatric diagnosis, but this candidate variable did not enter models estimating abstinence. Furthermore, follow-up was limited to 24 weeks, the sample was composed of moderate to heavy smokers and is not representative of most US Black smokers, and findings may have limited generalization to non-US Black participants and White participants.

Conclusions

US Black smokers in the EAGLES study were significantly less likely to quit than White smokers. Lower rates of abstinence were not explained by age, heaviness of smoking, treatment-related AEs, reduction in depression, and study drug compliance, which all favored Black smokers. To advance the important public health goal of reducing the prevalence of cigarette smoking, researchers and clinicians need to be aware that race is a proxy for powerful social and contextual factors that shape all aspects of life, including the likelihood of quitting smoking. Studies that identify race as a variable associated with abstinence do little to advance the field. Rather, prospectively designed studies are needed to identify the variables associated with race that make it harder for Black smokers to quit.

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SUPPLEMENT 1.

Trial Protocol

SUPPLEMENT 2.

eTable 1. Relation of Demographic, Smoking, Treatment Process, and Psychosocial Variables With Race and Continuous Abstinence Rates Weeks 9-24 for the Sample Overall

eTable 2. General Linear Regression Models Examining the Effects of Psychiatric Cohort, Treatment Group, Race, and Interactions on Continuous Abstinence Rates Weeks 9-24 and 9-12

eTable 3. Risk Differences and Odds Ratios From a Main Effects Model (Cohort, Race, and Treatment) for Continuous Abstinence Rates Weeks 9-24 and 9-12

eTable 4. Final Stepwise Logistic Regression Modeling of Continuous Abstinence Rates Weeks 9-24 With Baseline and Postbaseline Factors Modeled Separately

eTable 5. Relation of Demographic, Smoking, Treatment Process, and Psychosocial Variables With Race and Continuous Abstinence Rates Weeks 9-12 for the Sample Overall

eTable 6. Final Stepwise Logistic Regression Modeling of Continuous Abstinence Rates Weeks 9-12 With Baseline and Postbaseline Factors Modeled Separately

eTable 7. Final Stepwise Logistic Regression Modeling of Continuous Abstinence Rates Weeks 9-12 With Baseline and Postbaseline Factors Modeled Together

eFigure 1. 7-Day Point Prevalence Abstinence for Black and Whites by Treatment and Psychiatric Cohort

eFigure 2. Cigarettes per Day for Black and White Continuing Smokers by Treatment and Psychiatric Cohort

eReference

SUPPLEMENT 3.

Data Sharing Statement