

# Smoking Cessation Pharmacotherapy Efficacy in Comorbid Medical Populations: Secondary Analysis of the Evaluating Adverse Events in a Global Smoking Cessation Study (EAGLES) Randomized Clinical Trial

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## Abstract

**Introduction:** This study sought to compare medication efficacy in participants with medical comorbidities who smoke in the Evaluating Adverse Events in a Global Smoking Cessation Study (EAGLES) trial, a double-blind, triple-dummy, placebo- and active-controlled randomized controlled trial.

**Aims and Methods:** Participants were from the U.S. cohort of the main trial and randomized (1:1:1:1) to varenicline, bupropion, nicotine replacement therapy (NRT) patch, or placebo for 12 weeks with follow-up through week 24. Medical comorbidity data were derived from the baseline medical screening questionnaire and categorized into four subgroups (cardiac, respiratory, vascular, and diabetes). Within each comorbidity, generalized linear mixed models were used to assess the association between treatment and continuous abstinence rates from weeks 9–12 to 9–24. Similar models were used to test the effect of number of comorbidities on abstinence.

**Results:** Varenicline resulted in the highest week 12 abstinence rates across all pharmacotherapies and compared to placebo in all comorbidity subgroups: Cardiac (40.0% vs. 3.6%; odds ratios [OR] = 23.3 [5.1–107.1]), respiratory (24.7% vs. 12.8%; OR = 2.2 [1.3–3.8]), vascular (29.1% vs. 10.4%; OR = 3.6 [2.3–5.7]), and diabetes (30.9% vs. 8.3%; OR = 6.5 [2.3–19.0]). This was maintained at week 24 for those with cardiac (23.3% vs. 1.8%; OR = 21.7 [2.7–178.2]), vascular (18.9% vs. 7.1%; OR = 3.1 [1.8–5.3]), and diabetes (20.6% vs. 4.2%; OR = 8.4 [2.1–33.7]) comorbidities. Treatment contrasts within some comorbidity subgroups revealed superior efficacy of varenicline over other pharmacotherapies. All pharmacotherapies increased the odds of abstinence regardless of number of comorbidities.

**Conclusions:** Varenicline is the most efficacious option for patients with manageable cardiac, respiratory, vascular, and diabetes conditions to quit smoking, supporting recent clinical practice guidelines that recommend varenicline as first-line pharmacotherapy. Bupropion and NRT demonstrated efficacy for some comorbidity subgroups.

**Implications:** This secondary analysis of the EAGLES trial demonstrated that varenicline is the most efficacious option for patients with cardiac, respiratory, vascular, and diabetes diagnoses to quit smoking. This demonstration of varenicline efficacy among individuals with comorbid medical conditions supports recent clinical practice guidelines that recommend varenicline as a first-line pharmacotherapy for smoking cessation.

## Introduction

Cigarette smoking remains the leading cause of morbidity and mortality with more than 16 million people in the U.S. living with a smoking-related disease.<sup>1</sup> Smoking causes cancer, cardiovascular diseases, respiratory diseases, and diabetes.<sup>1</sup> Furthermore, conditions that are not necessarily caused by smoking (eg, psychiatric comorbidities, HIV) are still highly correlated with smoking and the associated health impacts for these populations are compounded.<sup>2</sup> Medical and psychiatric comorbidities present a complex issue for the treatment of smoking as well as treatment of the comorbidities. Many individuals with comorbidities may be interested in quitting smoking, but the comorbid disease may impact motivation

to quit, treatment response, and ability to quit smoking successfully.<sup>2</sup>

Clinical practice guidelines for treating tobacco use indicate that combination of behavioral and pharmacological approaches are most effective and can be offered to any person who smokes, including those with medical comorbidities (assuming no contraindications for pharmacological agents).<sup>3–6</sup> First-line pharmacotherapy options include varenicline and nicotine replacement therapy (NRT), which are routinely used in clinical practice to treat people who smoke with and without comorbidities. However, choice of pharmacotherapy may need to be tailored because of contraindications, comorbidities, and for specific populations.<sup>2,7</sup> Available smoking cessation pharmacotherapies may have differential effects across

comorbid populations, and research has yet to elucidate these effects. Exploring the efficacy of pharmacotherapies for medically complex patients has important implications for tobacco treatment clinical strategies and broader population generalizability.

The Evaluating Adverse Events in a Global Smoking Cessation Study (EAGLES) trial was a large, multi-site, placebo-controlled, randomized controlled trial examining the safety and efficacy of varenicline, bupropion, and NRT, for smoking cessation among individuals with ( $N = 4116$ ) and without ( $N = 4028$ ) psychiatric comorbidities.<sup>8</sup> This trial found that varenicline was more effective than placebo, NRT, and bupropion for smoking abstinence, whereas bupropion and nicotine patches were more effective than placebo. Importantly, this study demonstrated no significant increase in neuropsychiatric adverse events among those taking varenicline or bupropion relative to nicotine patches or placebo.<sup>8</sup> A secondary analysis of the EAGLES trial also demonstrated the cardiovascular safety of varenicline.<sup>9</sup> The EAGLES trial presents a unique opportunity to evaluate efficacy of these tobacco treatment pharmacotherapies among those who have medical and psychiatric comorbidities. The present study is a secondary analysis of the trial comparing (1) the efficacy of varenicline, bupropion, and NRT for people who smoke who are diagnosed with medical comorbidities and (2) the efficacy of varenicline, bupropion, and NRT for people who smoke with increasing numbers of medical comorbidities irrespective of type.

## Methods

### Design

This study is a secondary analysis of the EAGLES trial (ClinicalTrials.gov NCT01456936), a double-blind, triple-dummy, placebo-controlled, and active-controlled (NRT; 21 mg per day with taper), randomized (1:1:1:1) clinical trial of varenicline (1 mg twice daily) and bupropion (150 mg twice daily).<sup>8</sup> Enrolled participants were asked to set a quit date for 1 week following randomization into treatment arm and initiation of medication use. Participants were also given brief ( $\leq 10$  minutes) smoking cessation counseling at the onset of treatment and at each clinic visit. Study medications were administered for 12 weeks with a nontreatment follow-up through week 24. The protocol and consent documents were approved by the institutional review boards or ethics committees at each site. This secondary analysis was performed from October 2021 to June 2022. The data from U.S. sites were available from the primary trial sponsor (Pfizer) for the present analysis.

### Participants

U.S. participants ( $N = 4207$ ) in the primary EAGLES trial were individuals who smoked an average of ten or more cigarettes per day during the previous year (confirmed by exhaled breath carbon monoxide  $>10$  ppm at screening), aged 18–75 years, with and without prespecified psychiatric diagnoses, and who were motivated to stop smoking by accepting a set quit date as part of their participation in the trial. The primary trial excluded individuals who had severe medical comorbidities. A complete description of the inclusion and exclusion criteria can be found in the appendix of the primary publication.<sup>8</sup> Of relevance to the present study, participants were excluded if they had: (1) severe chronic obstructive pulmonary disease,

(2) clinically significant cardiovascular disease or cerebrovascular disease in the past 2 months, and (3) other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or interfere with the interpretation of study results. Despite excluding individuals with severe respiratory and cardiovascular disease, participants were still enrolled who had manageable medical conditions.

### Outcomes

The primary outcomes were continuous cigarette abstinence rate for weeks 9 to 12 and 9 to 24. Abstinence was defined as self-reported cigarette abstinence throughout the specified period, biochemically confirmed by exhaled carbon monoxide less than 10 ppm. Missing self-reported data was classified as smoking.

### Variables of Interest

Medical comorbidity variables were derived from the data on the medical screening questionnaire at baseline. Any present medical conditions endorsed by participants were recorded using their respective MedDRA Lowest Level Term code.<sup>10</sup> Using the Surgeon General's Report<sup>1</sup> as a guide for identifying conditions caused by smoking, six representative comorbidity classes were selected using the system organ class or high-level term MedDRA codes: Neoplasms; metabolism and nutrition disorders (diabetes mellitus type II only); respiratory, thoracic, and mediastinal disorders (eg, asthma); cardiac disorders (eg, atrial fibrillation, congestive heart failure); vascular disorders (eg, hypertension); and immune system disorders (rheumatoid arthritis and HIV only).

Psychiatric comorbidity was defined in the primary trial per the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR),<sup>11</sup> and included endorsement of any one of the following: History of suicidal ideation or behavior, history of a psychiatric diagnosis (defined as the primary diagnosis: None, mood disorder, anxiety disorder, psychotic disorder, or borderline personality disorder), or alcohol or substance abuse disorder via structured clinical interview. Because the parent study specifically aimed to evaluate differences in psychiatric comorbidity, this variable was included as a covariate in the present analysis.

Additional variables included biological sex, age, race, cigarettes per day in the month prior to enrollment, cigarette dependence (Fagerström Test for Cigarette Dependence),<sup>12</sup> age of starting smoking, length of time as smoker, lifetime serious quit attempts (yes or no and number), and discontinuation from the study drug. A new variable, number of comorbidities, was calculated from the medical data as described above. Each medical comorbidity listed in the baseline medical assessment was totaled for each participant and categorized (0, 1, 2, 3, 4, or  $\geq 5$ ).

### Statistical Analysis

Generalized linear mixed-effects models were utilized to determine the efficacy of varenicline, bupropion, and NRT on abstinence within each medical comorbidity group. We assessed linear contrast to estimate odds ratios (OR) and 95% confidence intervals (CI) for specific treatment contrasts; specifically, varenicline versus NRT, varenicline versus bupropion, NRT versus bupropion, and each versus placebo on abstinence outcomes (weeks 9 to 12 [end of treatment] and weeks 9 to 24 [follow-up]). Models included terms for

treatment group, cohort (non-psychiatric cohort and psychiatric cohort), sex (male and female), age (continuous values from 18 to 75), and race (white and nonwhite black, Asian, Hispanic, or Other). Of note, models were run that included a treatment X psychiatric cohort interaction term, as well as models that included a discontinuation of study drug term; however, these terms did not significantly change outcomes reported from the more parsimonious models and therefore are not reported.

Additional models assessed number of comorbidities (0 [reference], 1, 2, 3, 4, or  $\geq 5$ ), on end-of-treatment and follow-up abstinence outcomes for varenicline versus other treatments, with cohort, sex, age, and race as covariates. All statistical analyses were performed with SAS 9.4.

## Results

Trial findings were reported following the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline for RCTs and a diagram is presented in [Supplementary Figure 1](#). The present analysis includes 4151 (98.7%) individuals from the U.S. sites who had complete medical history data at the baseline screening assessment. Of those in this final analytic sample,  $n = 2359$  (56.8%) were classified into the psychiatric cohort and  $n = 1792$  (43.2%) were in the non-psychiatric cohort.

### Comorbidities

Individuals with severe medical and psychiatric comorbidities were excluded from the primary study. As such, although cancer, rheumatoid arthritis, and HIV were included in the initial assessment of self-reported medical comorbidities at baseline, the case counts were small and too low for inclusion in the planned analyses ( $N_s = 77, 34,$  and  $24$ , respectively). Of the 4151 participants evaluated in the present study, 252 had documented cardiac conditions (6.07%), 817 had respiratory conditions (19.68%), 1,211 had vascular conditions (29.17%), and 282 had diabetes (6.79%). Individuals could have been in multiple comorbidity categories. In the overall sample, 2317 (55%) reported zero medical comorbidities, 1,148 (27.66%)

reported 1, 434 (10.46%) reported 2, 152 (3.66%) reported 3, 56 (1.35%) reported 4, and 44 (1.05%) had 5 or more comorbidities. Participant demographics by medical condition are presented in [Supplementary Table 1](#).

### Cigarette Abstinence

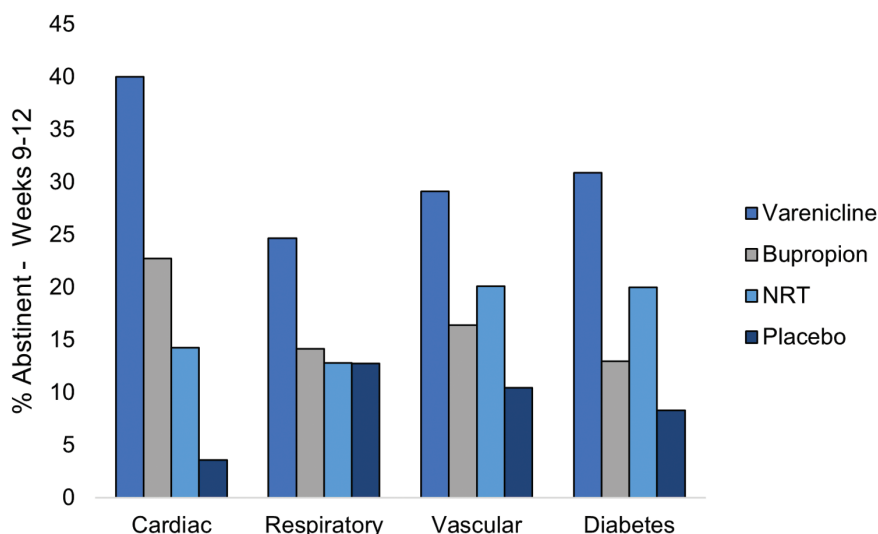
Abstinence rates by treatment arm and condition are presented in [Figure 1](#) (week 12) and [Figure 2](#) (week 24), and the full models are presented in [Table 1](#) (week 12) and [Table 2](#) (week 24). Varenicline demonstrated superior efficacy in nearly every comparison across disease groups.

### Cardiac Conditions

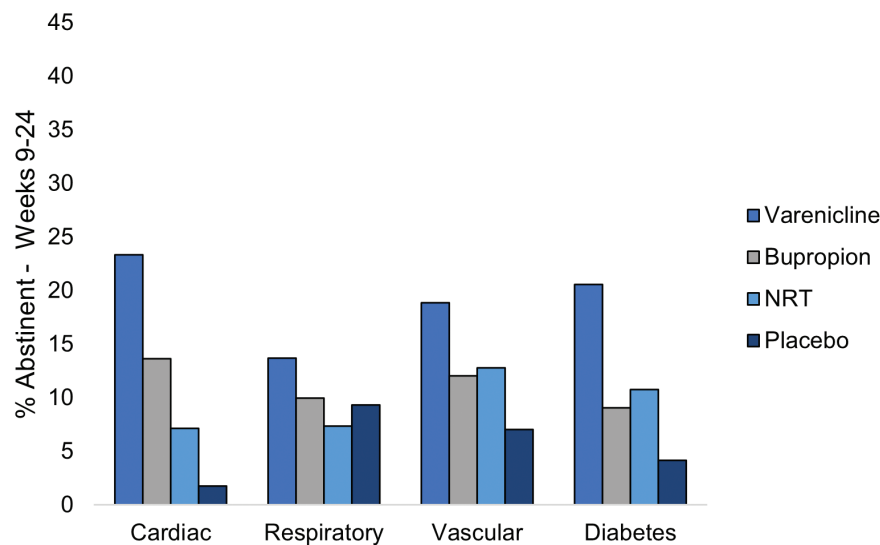
For individuals with cardiac conditions, those in the varenicline arm were more likely to be abstinent (40.0%) compared to those in the bupropion (22.7%; odds ratio [OR] = 2.4, 95% confidence interval [CI] [1.1, 5.3]), NRT (14.3%; OR = 3.7, 95% CI [1.5, 9.2]), and placebo (3.6%; OR = 23.3, 95% CI [5.1, 107.1]) arms at week 12. At week 24, those in the varenicline arm were more likely to be abstinent (23.3%) compared to those in the NRT (7.1%; OR = 3.9, 95% CI [1.2, 12.3]) and placebo (1.8%; OR = 21.7, 95% CI [2.7, 178.2]) arms. Furthermore, at week 12, those randomized to bupropion were more likely to be abstinent compared to placebo (OR = 9.1, 95% CI [1.9, 43.0]), and those randomized to NRT were more likely to be abstinent compared to placebo (OR = 16.8, 95% CI [2.1, 137.3]). At week 24, bupropion continued to produce higher abstinence rates compared to placebo (OR = 10.4, 95% CI [1.2, 90.4]).

### Respiratory Conditions

For individuals with respiratory conditions, those in the varenicline arm were more likely to be abstinent (24.7%) compared to those in the bupropion (14.1%; OR = 2.0, 95% CI [1.2, 3.4]), NRT (12.8%; OR = 2.3, 95% CI [1.4, 3.9]), and placebo (12.8%; OR = 2.2, 95% CI [1.3, 3.8]) arms at week 12. At week 24, those in the varenicline arm were more likely to be abstinent (13.7%) compared to those in the NRT (7.4%; OR = 2.1, 95% CI [1.1, 4.0]) arms but not compared to placebo.



**Figure 1.** Week 12 continuous abstinence rates by medical comorbidity and treatment group.



**Figure 2.** Week 24 continuous abstinence rates by medical comorbidity and treatment group.

### Vascular Conditions

For individuals with vascular conditions, those in the varenicline arm were more likely to be abstinent (29.1%) compared to those in the bupropion (16.4%; OR = 2.1, 95% CI [1.4, 3.2]), NRT (20.1%; OR = 1.6, 95% CI [1.1, 2.4]) and placebo (10.4%; OR = 3.6, 95% CI [2.3, 5.7]) arms at week 12. At week 24, those in the varenicline arm were more likely to be abstinent (18.9%) compared to those in bupropion (12.0%; OR = 1.7, 95% CI [1.1, 2.7]), NRT (12.8%; OR = 1.6, 95% CI [1.0, 2.5]) and placebo (7.1%; OR = 3.1, 95% CI [1.8, 5.3]) arms. Furthermore, at week 12, those randomized to NRT were more likely to be abstinent compared to placebo (OR = 2.1, 95% CI [1.3, 3.3]) which was maintained at week 24 (OR = 1.9, 95% CI [1.1, 3.3]).

### Diabetes

For individuals with diabetes, those in the varenicline arm were more likely to be abstinent (30.9%) compared to those in the bupropion (13.0%; OR = 3.4, 95% CI [1.4, 8.1]) and placebo (8.3%; OR = 6.5, 95% CI [2.3, 19.0]) arms at week 12. At week 24, those in the varenicline arm were more likely to be abstinent (20.6%) compared to those in bupropion (9.1%; OR = 3.0, 95% CI [1.1, 8.3]) and placebo (4.12%; OR = 8.4, 95% CI [2.1, 33.7]) arms. Furthermore, at week 12, those randomized to NRT were more likely to be abstinent compared to placebo (OR = 3.2, 95% CI [1.0, 10.3]).

### Number of Comorbidities

The effect of treatment and number of medical comorbidities on abstinence rates is presented in Table 3. The total number of health comorbidities did not affect abstinence outcomes at week 12 ( $F_{5, 4137} = 0.80$ ) or week 24 ( $F_{5, 4137} = 1.89$ ). All pharmacotherapies increased the odds of abstinence, relative to placebo, regardless of number of comorbidities.

## Discussion

This secondary analysis of the EAGLES trial demonstrated that varenicline is the most efficacious option for patients with manageable cardiac, respiratory, vascular, and diabetes conditions to quit smoking. Superior efficacy was observed

for varenicline compared to bupropion and placebo for week 12 abstinence across all comorbid disease categories, and superior efficacy compared to NRT across 3 conditions. At week 24, abstinence rates for varenicline were higher compared to placebo in the cardiac, vascular, and diabetes groups. Bupropion demonstrated superior efficacy compared to placebo among those with cardiac conditions at weeks 12 and 24. NRT demonstrated superior efficacy compared to placebo among cardiac, vascular, and diabetes groups at week 12, and this effect was maintained for those with vascular conditions at week 24. A study being conducted simultaneously found similar outcomes in the international EAGLES dataset, lending support to the consistency and reproducibility of these findings.<sup>13</sup> The present study included individuals with past or present alcohol dependence and used age, race, and sex as covariates.

This demonstration of varenicline efficacy among individuals with manageable comorbid medical conditions supports recent clinical practice guidelines that recommend varenicline as a first-line pharmacotherapy for smoking cessation.<sup>4,6</sup> In light of potential side effects and contraindications to varenicline, the finding that bupropion and NRT increase quit rates compared to placebo at week 24 in certain comorbidity groups is promising as an alternative. As the number of comorbidities increases, any of the pharmacotherapy options increases the odds of abstinence, demonstrating that medically complex individuals benefit from smoking cessation pharmacotherapy. Consistent with the primary publication findings, abstinence rates tended to decrease across all study arms by week 24. Some comorbidity subgroups had abstinence rates for specific pharmacotherapies that were greater than placebo at week 12, but those trends did not maintain at week 24. This finding may reflect the general trend of relapse over time, but may also highlight comorbidity-specific challenges with maintaining abstinence (eg, high medical stress, comorbidity symptom burden, etc.). Relapse prevention remains an important issue among all individuals who smoke, especially those with comorbidities who may require additional cessation support.

The differential effects of these medications are relevant for potential tailored treatment approaches, especially if varenicline is not tolerated. Individuals with medical and

**Table 1.** Twelve-Week Abstinence by Treatment

Abstinence rates by treatment	Cardiac N = 252		Respiratory N = 817		Vascular N = 1211		Diabetes N = 282	
	Treatment n	Abstinent n (20.24%)	Treatment n	Abstinent n (16.28%)	Treatment n	Abstinent n (19.08%)	Treatment n	Abstinent n (17.73%)
Varenicline	60	24 (40.00%)	219	54 (24.66%)	302	88 (29.14%)	68	21 (30.88%)
Bupropion	66	15 (22.73%)	191	27 (14.14%)	299	49 (16.39%)	77	10 (12.99%)
NRT	70	10 (14.29%)	203	26 (12.81%)	313	63 (20.13%)	65	13 (20.00%)
Placebo	56	2 (3.57%)	204	26 (12.75%)	297	31 (10.44%)	72	6 (8.33%)
Full model-treatment effect	Type III F (DF)	Type III F (DF)	Type III F (DF)	Type III F (DF)	Type III F (DF)	Type III F (DF)	Type III F (DF)	Type III F (DF)
	6.98 (3, 244)	5.23 (3, 809)	11.36 (3, 1203)	4.84 (3, 274)				
Individual treatment estimates (treatment   reference)	$\beta$	Type III F	OR (95%CI)	Type III F	$\beta$	Type III F	OR (95%CI)	Type III F
Varenicline	0.86	4.68	2.38 (1.08 to 5.25)	7.23	0.75	13.75	2.12 (1.42 to 3.16)	7.37
NRT	1.31	8.06	3.69 (1.48 to 9.18)	10.01	0.49	6.48	1.63 (1.11 to 2.37)	2.60
Placebo	3.15	16.69	23.29 (5.06 to 107.08)	9.42	1.28	30.86	3.61 (2.29 to 5.67)	12.21
Bupropion	0.29	0.36	1.33 (0.52 to 3.44)	0.41	-0.24	1.29	0.79 (0.52 to 1.19)	1.49
Placebo	2.21	7.82	9.05 (1.91 to 42.97)	0.13	0.48	3.65	1.61 (0.98 to 2.62)	0.85
NRT	2.82	7.10	16.84 (2.07 to 137.31)	0.02	0.73	9.37	2.08 (1.30 to 3.33)	4.00
Placebo								3.23 (1.01 to 10.27)

% abstinent represent column %s. Full models included age, race, sex, and psychiatric cohort. Italics results indicate  $p < .05$ . Additional models were run with treatment\*cohort interaction term, which did not produce significant findings and thus were not reported.

**Table 2.** Twenty-Four-week Abstinence by Treatment

Abstinence rates by treatment	Cardiac N = 252		Respiratory N = 817		Vascular N = 1211		Diabetes N = 282		
	Treatment n	Abstinent n = 29 (11.51%)	Treatment n	Abstinent n = 83 (10.16%)	Treatment n	Abstinent n = 154 (12.72%)	Treatment n	Abstinent n = 31 (10.99%)	
Varenicline	60	14 (23.33%)	219	30 (13.70%)	302	57 (18.87)	68	14 (20.59%)	
Bupropion	66	9 (13.64%)	191	19 (9.95%)	299	36 (12.04%)	77	7 (9.09%)	
NRT	70	5 (7.14%)	203	15 (7.39%)	313	40 (12.78%)	65	7 (10.77%)	
Placebo	56	1 (1.79%)	204	19 (9.31%)	297	21 (7.07%)	72	3 (4.17%)	
Full model-treatment effect	Type III F (DF)		Type III F (DF)		Type III F (DF)		Type III F (DF)		
	3.84 (3, 244)		1.71 (3, 809)		5.98 (3, 1203)		3.76 (3, 274)		
Individual treatment estimates (treatment   reference)	$\beta$	Type III F	OR (95%CI)	Type III F	OR (95%CI)	Type III F	OR (95%CI)	Type III F	OR (95%CI)
Varenicline	0.73	2.34	2.08 (0.81 to 5.38)	1.46	1.46 (0.78 to 2.70)	0.55	1.73 (1.09 to 2.74)	1.09	4.50 (1.08 to 8.32)
NRT	1.35	5.38	3.86 (1.21 to 12.26)	4.63	2.06 (1.06 to 3.98)	0.45	1.58 (1.01 to 2.46)	0.86	2.69 (0.84 to 6.77)
Placebo	3.08	8.39	21.74 (2.65 to 178.23)	1.98	1.55 (0.84 to 2.89)	1.12	3.08 (1.80 to 5.25)	2.13	9.28 (2.11 to 33.65)
Bupropion	NRT	0.36	1.44 (0.43 to 4.89)	0.44	1.43 (0.75 to 3.21)	-0.07	0.94 (0.58 to 1.52)	-0.23	0.16 (0.25 to 2.52)
Placebo	Placebo	2.34	4.59 (1.19 to 90.36)	0.06	0.04 (0.54 to 2.11)	0.54	1.71 (0.96 to 3.03)	0.62	0.70 (0.43 to 8.13)
NRT	Placebo	2.24	3.12 (0.76 to 114.93)	-0.32	0.77 (0.35 to 1.49)	0.62	1.87 (1.06 to 3.27)	1.28	2.60 (0.75 to 17.52)

% abstinent represent column %s. Full models included age, race, sex, and psychiatric cohort. Italics results indicate  $p < .05$ . Additional models were run with treatment\*cohort interaction term, which did not produce significant findings and thus were not reported.

**Table 3.** Effect of Treatment and Number of Medical Health Conditions on Abstinence Rates

Twelve-week				
Full model effects		Type III F (DF)		
Treatment		33.97 (3, 4141)		
# of Health Conditions		0.80 (5, 4137)		
Individual Treatment Estimates (treatment   reference)		$\beta$	Type III F	OR (95%CI)
Varenicline	Bupropion	0.58	28.13	1.79 (1.44 to 2.22)
	NRT	0.55	25.67	1.74 (1.40 to 2.15)
	Placebo	1.27	97.21	3.58 (2.78-4.62)
Bupropion	NRT	-0.02	0.03	0.98 (0.77 to 1.23)
	Placebo	0.69	25.95	2.01 (1.53 to 2.63)
NRT	Placebo	0.70	26.85	2.02 (1.54 to 2.64)
Twenty-four-week				
Full model effects		Type III F (DF)		
Treatment		15.11 (3, 4141)		
# of Health Conditions		1.89 (5, 4137)		
Individual Treatment Estimates (treatment   reference)		$\beta$	Type III F	OR (95%CI)
Varenicline	Bupropion	0.38	8.67	1.47 (1.14 to 1.89)
	NRT	0.47	12.87	1.61 (1.24 to 2.08)
	Placebo	1.01	43.68	2.74 (2.03 to 3.69)
Bupropion	NRT	0.10	0.53	1.11 (0.84 to 1.46)
	Placebo	0.63	15.42	1.88 (1.37 to 2.57)
NRT	Placebo	0.52	10.55	1.69 (1.23 to 2.32)

Full model included age, race, sex, and psychiatric cohort. Health condition categories included 0, 1, 2, 3, 4,  $\geq 5$  (0 as reference). Italics results indicate  $p < .01$ .

ipsychiatric comorbidities may be taking other pharmacological agents that are contraindicated with varenicline, or use of varenicline may result in elevated liver enzymes that would warrant discontinuation. Some individuals have also reported allergic reactions (ie, skin rash) when taking varenicline, although these allergies are relatively rare. In these instances, selecting bupropion or NRT may be preferable and these data may help to guide those clinical choices.

In general, the individuals selected for participation in the EAGLES trial were healthy sample because of the parent trial exclusion criteria. The results of the present publication should be replicated among those with more significant comorbidities. Participants in the parent trial were mostly white (82%) and results should be replicated with more diverse samples, especially given that there are clear racial disparities among many comorbid medical conditions. Of note, for those receiving NRT, only patches were given. Dual NRT or other combination therapy (eg, varenicline plus NRT) may have different efficacy profiles in these subgroups. Furthermore, the study was not powered to assess differences in comorbid conditions. Small sample sizes mean high variability in estimates as seen by large CI (eg, in the cardiac condition when placebo was used as the reference), and intent-to-treat analyses have inherent limitations.<sup>14</sup>

Patients with medical comorbidities face an urgent need to quit smoking for the management of their condition as well as their long-term health. Coupled with the existing neuropsychiatric and cardiovascular safety data,<sup>8,9</sup> the present study is not only practice confirming for providers already prescribing varenicline but will likely be practice changing for those who are unsure

of best treatment options for their medically complex patients. Treating individuals with comorbidities who smoke should be a regular part of the clinical care plan for the comorbid condition. For example, managing hypertension in the clinic should include referral to tobacco treatment behavioral support programs and prescription of varenicline just as a provider would prescribe antihypertensives and diet modifications. Beyond replicating the present study's findings, future research should leverage implementation science approaches to optimize tobacco treatment delivery in the context of medical comorbidities.

## Supplementary Material

A Contributorship Form detailing each author's specific involvement with this content, as well as any supplementary data, are available online at <https://academic.oup.com/ntr>.

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## Declaration of Interest

Dr. Toll testifies on behalf of plaintiffs who have filed litigation against the tobacco industry.

## Author Contributions

Alana Rojewski (Conceptualization [Lead], Supervision [Lead], Writing – original draft [Equal], Writing – review & editing [Equal]), Amanda Palmer (Conceptualization [Supporting], Data curation [Lead], Formal analysis [Lead], Writing – original draft [Equal], Writing – review & editing [Equal]), Nathaniel Baker (Formal analysis [Supporting], Writing – review & editing [Equal]), and Benjamin Toll (Conceptualization [Supporting], Writing – review & editing [Equal]).

## Data Availability

The authors of the present manuscript obtained the data through request from Vivli Inc., a third party responsible for managing the study sponsor (Pfizer) data. We are unable to make data-sharing decisions. The code used in this secondary analysis are available by request to the authors.

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