Neuropsychiatric Safety and Efficacy of Varenicline, Bupropion, and Nicotine Patch in Smokers With Psychotic, Anxiety, and Mood Disorders in the EAGLES Trial

A. Eden Evins, MD, MPH, Neal L. Benowitz, MD,† Robert West, PhD,‡ Cristina Russ, MD,§ Thomas McRae, MD, MS,§ David Lawrence, PhD,§ Alok Krishen, MS,||¶ Lisa St Aubin, DVM,§ Melissa Culhane Maravic, PhD, MPH,# and Robert M. Anthenelli, MD***

Abstract:

Background: Neuropsychiatric safety and relative efficacy of varenicline, bupropion, and transdermal nicotine patch (NRT) in those with psychiatric disorders are of interest.

Methods: We performed secondary analyses of safety and efficacy outcomes by psychiatric diagnosis in EAGLES (Evaluating Adverse Events in a Global Smoking Cessation Study), a 12-week, randomized, double-blind, triple-dummy, placebo- and active (NRT)–controlled trial of varenicline and bupropion with 12-week follow-up, in a subset population, n = 4092, with a primary psychotic (n = 390), anxiety (n = 792), or mood (n = 2910) disorder. Primary end-point parameters were incidence of prespecified moderate and severe neuropsychiatric adverse events (NPSAEs) and weeks 9 to 12 continuous abstinence rates (9–12CAR).

Results: The observed NPSAE incidence across treatments was 5.1% to 6.3% in those with a psychotic disorder, 4.6% to 8.0% in those with an anxiety disorder, and 4.6% to 6.8% in those with a mood disorder. Neither varenicline nor bupropion was associated with significantly increased NPSAEs relative to NRT or placebo in the psychiatric cohort or any psychiatric diagnostic subcohort. There was a significant effect of treatment on 9–12CAR ($P < 0.0001$) and no significant treatment-by-diagnostic subcohort interaction ($P = 0.24$). Abstinence rates with varenicline were superior to bupropion, NRT, and placebo, and abstinence with bupropion and NRT was superior to placebo. Within-diagnostic subcohort comparisons of treatment efficacy yielded estimated odds ratios for 9–12CAR versus placebo of greater than 3.00 for varenicline, greater than 1.90 for bupropion, and greater than 1.80 for NRT for all diagnostic groups.

Conclusions: Varenicline, bupropion, and nicotine patch are well tolerated and effective in adults with psychotic, anxiety, and mood disorders. The relative effectiveness of varenicline, bupropion, and NRT versus placebo did not vary across psychiatric diagnoses.

Key Words: anxiety, bupropion, mood, schizophrenia, smoking cessation, varenicline

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Despite strong evidence for efficacy of first-line pharmacotherapies for smoking cessation in those with psychotic (PD) and mood disorders (MD),[1–10] smoking prevalence remains higher and is declining more slowly in those with mental health conditions than in the general population,[11–14] with 1 in 3 cigarettes in the United States and United Kingdom sold to someone with a mental illness.[13,15] Despite the fact that the mortality gap, largely due to smoking-related illness, for those with a serious mental illness compared with those in the general population is large and growing,[16–18] pharmacotherapeutic cessation aids are underutilized in those with mental illness, arguably due at least in part to neuropsychiatric (NPS) safety concerns.[13,19–27] The health benefit of smoking cessation is clear[28,29]; thus, assessment of relative NPS safety and efficacy of smoking cessation pharmacotherapies in large samples of smokers with psychiatric illness is needed by clinicians, policy makers, and patients in order to clarify their benefit-to-risk ratio.

Evaluating Adverse Events in a Global Smoking Cessation Study (EAGLES; NCT01456936) was a large, randomized controlled trial to evaluate NPS safety and efficacy of varenicline and bupropion compared with placebo and transdermal nicotine patch (NRT) for smoking cessation in adults with and without psychiatric illness.[30] In the overall EAGLES study population, neither varenicline nor bupropion had significantly greater risk of neuropsychiatric adverse events (NPSAEs) than NRT or placebo, whereas those assigned to varenicline had significantly superior continuous abstinence rates (CARs) to those on bupropion, NRT, or placebo, and those assigned to bupropion and NRT had superior CARs to those on placebo. In the primary report of this study, those with a lifetime psychiatric illness were reported in aggregate to have no difference in relative treatment safety or efficacy than those without a psychiatric illness.[30] Random assignment to study medication in the EAGLES psychiatric cohort was stratified according to prespecified diagnostic categories, those with PD, anxiety disorder (AD), and MD.

In order to inform treatment decision making for smokers with PD, AD, and MD, the primary aim of this analysis was to estimate the NPSAE rate with varenicline, bupropion, transdermal NRT patch, and placebo in smokers with PD, AD, and MD. Further, we sought to compare the efficacy for continuous tobacco abstinence from study week 9 to the end of treatment (9–12CAR) and to the 6-month follow-up (9–24CAR) for these treatments within these diagnostic categories. We addressed these aims while assessing the impact of patient-level factors: comorbid substance

From the *Department of Psychiatry, Harvard Medical School and Massachusetts General Hospital Boston, MA; †Department of Medicine, University of California, San Francisco, CA; ‡Department of Behavioural Science and Health, University College London, London, United Kingdom; §Pfizer, New York, New York; ||PAREXEL International on behalf of GSK, Research Triangle Park, NC; ¶Division of Biostatistics, Harvard Medical School and Massachusetts General Hospital; #Department of Psychiatry, Massachusetts General Hospital, Boston, MA; and **Department of Psychiatry, University of California, San Diego, CA.

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Reprints: A. Eden Evins, MD, MPH, Massachusetts General Hospital Center for Addiction Medicine, 101 Merrimac St, Suite 320, Boston, MA 02114 (e-mail: aeevins@mgh.harvard.edu).

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use disorder (SUD), severity of nicotine dependence, and sex, previously reported to impact smoking cessation success.[31–33] While the primary aim of the article was estimation of NPSAE rates in the diagnostic by treatment subgroups outlined, for the abstinence aim, it was our hypothesis that varenicline would be associated with higher rates of smoking cessation than NRT or bupropion, and all active treatments would be associated with superior abstinence rates to placebo in all 3 diagnostic groups.

MATERIALS AND METHODS

Study Design

EAGLES was a multinational, multicenter, randomized, double-blind, placebo- and active (NRT)–controlled trial, conducted between November 2011 and January 2015. The primary report provides full details of the study design and primary outcomes.[30]

Participants

Eligible participants for the psychiatric cohort were adults, aged 18 to 75 years, who smoked 10 or more cigarettes per day, with exhaled carbon monoxide (CO) of more than 10 parts per million (ppm) at screening, were motivated to stop smoking, met *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision*[34] diagnostic criteria for current or lifetime PDs including schizophrenia and schizoaffective disorders; ADs including panic disorder, with or without agoraphobia, posttraumatic stress disorder, obsessive-compulsive disorder, social phobia, and generalized AD; MDs including major depressive disorder (MDD) or bipolar disorder; or borderline personality disorder. Those with qualifying primary psychiatric disorders were not excluded for other psychiatric comorbidities, but those secondary allowable diagnoses were also prespecified and excluded destabilizing psychiatric conditions such as alcohol and other drug use disorders within the previous 12 months. Because bupropion use in bipolar disorder was not allowed in European Union countries per prescribing guidelines, potential participants with bipolar disorder were excluded at the EU study sites. Smokers with a primary diagnosis of borderline personality disorder were enrolled; however, this subcohort was small (24 participants) and thus not included in these analyses. To operationalize clinical stability required for enrollment, the following were exclusionary: Clinical Global Impression Severity rating of 5 or greater (ie, markedly ill with intrusive symptoms that impair social/occupational function or cause intrusive levels of distress),[35] exacerbation of psychiatric condition in the prior 6 months, change in psychiatric medication or dose in the prior 3 months, active suicidal ideation with intent or plan as assessed with item 5 of the Columbia-Suicide Severity Rating Scale (C-SSRS), suicidal behavior in the prior 12 months as assessed with the C-SSRS or considered by the investigator to be at imminent risk of suicidal or self-injurious behavior, active SUD in the prior 12 months, and urine drug screen positive for nonprescribed addictive drugs.

Randomization, Masking, and Study Treatment

Computer-generated randomized assignment to varenicline 1 mg twice daily, bupropion sustained release 150 mg twice daily, NRT 21 mg/d with taper, or placebo was done in a 1:1:1:1 ratio with block size of 8 for each diagnostic subcohort (PD, AD, and MD) by-region combination in a triple-dummy (each participant not in the placebo arm received 1 active and 2 placebo treatments, eg, 1 patch and 2 pills per day, each pill to be taken bid) parallel-group design for 12-week treatment and 12-week follow-up phases. Participants and research personnel were blinded to treatment assignments.

Participants set a target quit date 1 week after randomization, coinciding with the end of varenicline and bupropion up-titration and initiation of NRT. Ten-minute individual smoking cessation counseling was provided at each study visit.[36] Study visits were weekly for 6 weeks, biweekly for 6 weeks, then at weeks 13, 16, 20, and 24. Telephone contacts to determine smoking status were conducted weekly between study visits. Participants were encouraged to complete all study visits even if treatment was discontinued.

Outcomes

Safety

The primary safety end point was occurrence of at least 1 treatment-emergent severe (significant interference with functioning) adverse event of anxiety, depression, feeling abnormal or hostility, and/or a moderate (some interference with functioning) or severe adverse event of agitation, aggression, delusions, hallucinations, homicidal ideation, mania, panic, paranoia, psychosis, suicidal ideation, suicidal behavior, or completed suicide. The primary end point was met when participants reported 1 or more event that coded to any of the predefined Medical Dictionary for Regulatory Activities (MedDRA, v.18.0)–derived preferred terms across these 16 symptom categories during treatment or within 30 days of treatment discontinuation. Severity criteria for the primary NPSAE outcome were prespecified; anxiety, depression, feeling abnormal, and hostility were required to be severe only to try to distinguish them from events that were expected to be common during cessation attempts.

Secondary safety end points included incidence of each component of the primary NPSAE end point and all that were rated as severe, Hospital Anxiety and Depression Scale (HADS) ratings,[37] and reports of suicidal ideation or behavior elicited by the C-SSRS.[38]

Efficacy

The main efficacy end point was CAR for weeks 9 to 12 (9–12CAR). To meet the end point, participants were considered abstinent at a study visit who reported tobacco abstinence since the previous study visit at each weekly visit from weeks 9 to 12 and to have had expired CO concentration of 10 ppm or less at in-clinic study visits (weeks 10 and 12). Participants who discontinued the study or were lost to follow-up through week 12 were considered nonabstinent. The secondary efficacy end point was CAR for weeks 9 to 24 (9–24CAR), defined similarly, that is, reported abstinence since the previous visit at each weekly visit from weeks 9 to 24 and CO concentrations of less than 10 ppm at in-clinic study visits (weeks 10, 12, 13, 16, 20, and 24), with subjects who discontinued the study or were lost to follow-up through week 24 considered nonabstinent.

Assessments

Psychiatric diagnosis was assessed at screening with the Structured Clinical Interviews for *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* Axis I and II Disorders.[34,39] Severity of cigarette dependence was assessed with the Fagerström Test for Cigarette Dependence (FTCD).[40] Neuropsychiatric adverse events were assessed at each study visit with open-ended questions, direct observation, and the semistructured Neuropsychiatric Adverse Events Interview (NAEI).[1,30] Positive responses on the NAEI were evaluated for frequency, duration, and severity to determine if they were NPSAEs.

TABLE 1. Baseline Demographic and Clinical Characteristics

	PDs (n = 386)				ADs (n = 782)				MDs (n = 2882)			
	Varenicline (n = 95)	Bupropion (n = 96)	NRT (n = 99)	Placebo (n = 96)	Varenicline (n = 193)	Bupropion (n = 200)	NRT (n = 195)	Placebo (n = 194)	Varenicline (n = 731)	Bupropion (n = 716)	NRT (n = 713)	Placebo (n = 722)
Female sex	34 (35.8)	32 (33.3)	38 (38.4)	34 (35.4)	116 (60.1)	124 (62.0)	123 (63.1)	110 (56.7)	479 (65.5)	470 (65.6)	466 (65.4)	482 (66.8)
Age, y	44.6 (11.6)	44.6 (10.7)	43.3 (10.2)	45.3 (9.6)	45.7 (11.6)	45.2 (12.1)	46.0 (11.0)	44.7 (12.5)	48.0 (11.7)	47.4 (12.4)	48.8 (11.5)	47.7 (11.3)
Race												
White	59 (62.1)	58 (60.4)	63 (63.6)	65 (67.7)	172 (89.1)	171 (85.5)	169 (86.7)	165 (85.1)	611 (83.6)	582 (81.3)	564 (79.1)	589 (81.6)
Black	33 (34.7)	36 (37.5)	31 (31.3)	26 (27.1)	17 (8.8)	21 (10.5)	18 (9.2)	21 (10.8)	95 (13.0)	108 (15.1)	126 (17.7)	108 (15.0)
Asian*	1 (1.1)	2 (2.1)	1 (1.0)	1 (1.0)	0 (0.0)	1 (0.5)	1 (0.5)	0 (0.0)	4 (0.5)	7 (1.0)	9 (1.3)	6 (0.8)
Other/unspecified*	2 (2.1)	0 (0.0)	4 (4.0)	4 (4.2)	4 (2.1)	7 (3.5)	7 (3.6)	7 (3.6)	21 (2.9)	19 (2.7)	14 (2.0)	19 (2.6)
Weight, kg	91.7 (25.9)	89.1 (22.0)	87.9 (21.7)	87.3 (22.1)	80.3 (20.2)	80.9 (22.9)	79.8 (21.5)	80.0 (20.9)	82.6 (20.9)	82.0 (20.6)	80.1 (19.3)	82.9 (21.2)
Smoking characteristics												
FTCD score, mean (SD)	6.8 (1.9)	6.9 (1.6)	6.8 (2.0)	7.0 (1.7)	5.9 (2.1)	5.9 (2.0)	6.0 (2.0)	5.8 (2.3)	6.0 (1.9)	6.0 (1.9)	5.8 (1.9)	5.8 (1.9)
Duration of smoking, mean (SD), y	26.1 (12.4)	26.6 (11.4)	24.9 (11.1)	25.9 (10.7)	27.3 (11.3)	27.1 (12.2)	28.1 (10.8)	26.2 (12.2)	29.7 (11.8)	28.8 (12.6)	29.7 (12.1)	29.2 (11.5)
Cigarettes smoked per day in past month, mean (SD)	22.5 (9.4)	21.9 (7.2)	23.9 (14.9)	24.3 (9.6)	20.8 (7.5)	20.5 (8.2)	22.0 (8.8)	21.3 (8.1)	20.2 (7.9)	20.4 (8.3)	20.0 (7.9)	20.0 (7.9)
Prior quit attempts, mean (SD)	2.2 (3.2)	1.9 (2.1)	2.2 (2.8)	3.2 (6.4)	3.1 (4.8)	3.5 (6.9)	2.5 (3.5)	2.9 (3.9)	3.6 (8.7)	3.8 (7.3)	3.8 (5.9)	3.9 (12.6)
Participants with ≥1 prior quit attempt, n (%)	67 (70.5)	70 (72.9)	71 (71.7)	69 (71.9)	163 (84.5)	169 (84.5)	156 (80.0)	168 (86.6)	620 (84.8)	602 (84.1)	622 (87.2)	614 (85.0)
Comorbid Axis I diagnosis	39 (41.1)	28 (29.2)	35 (35.4)	39 (40.6)	78 (40.4)	89 (44.5)	93 (47.7)	77 (39.7)	232 (31.7)	248 (34.6)	254 (35.6)	249 (34.5)
Prior SUD	32 (33.7)	22 (22.9)	20 (20.2)	30 (31.3)	42 (21.8)	43 (21.5)	46 (23.6)	39 (20.1)	150 (20.5)	168 (23.5)	168 (23.6)	172 (23.8)
Lifetime suicide-related behavior from CSSRS												
Suicidal ideation	25 (26.3)	28 (29.2)	31 (31.3)	27 (28.1)	34 (17.6)	48 (24.0)	45 (23.1)	45 (23.2)	275 (37.6)	277 (38.7)	252 (35.3)	275 (38.1)
Suicidal behavior	15 (15.8)	19 (19.8)	22 (22.2)	14 (14.6)	8 (4.1)	13 (6.5)	12 (6.2)	11 (5.7)	110 (15.0)	108 (15.1)	72 (10.1)	97 (13.4)
HADS scores												
Anxiety subscale score	4.6 (4.0)	5.2 (4.0)	5.5 (4.5)	4.9 (3.8)	5.5 (3.8)	5.6 (3.6)	5.5 (4.3)	5.8 (3.9)	5.0 (3.8)	5.2 (4.1)	5.0 (3.8)	5.0 (3.7)
Depression subscale score	4.0 (3.6)	4.1 (2.8)	3.8 (3.3)	3.7 (3.0)	2.6 (2.9)	2.9 (3.3)	3.0 (3.4)	2.6 (2.8)	3.2 (3.3)	3.4 (3.6)	3.2 (3.2)	3.1 (3.2)
Using psychotropic medication	94 (98.9)	92 (95.8)	95 (96.0)	94 (97.9)	114 (59.1)	109 (54.5)	109 (55.9)	94 (48.5)	395 (54.0)	347 (48.5)	354 (49.6)	364 (50.4)

*Asian and other/unspecified categories were combined for use in model.

Psychiatric symptom severity was also assessed at each study visit with HADS[37] and C-SSRS,[38] and tobacco and nicotine use was assessed with a structured questionnaire and expired CO measurement. Investigators evaluated whether positive responses on the C-SSRS or proxy reports from family members or others were NPSAEs.

Statistical Analysis

This is a secondary analysis of safety and efficacy of varenicline and bupropion compared with NRT and placebo in those with PD, AD, and MD within the EAGLES psychiatric cohort. The study was sized to assess treatment safety and efficacy within the overall psychiatric cohort that comprised these subcohorts, not within the subcohorts. The safety and efficacy end points were analyzed using generalized linear models (binomial; identity link for safety, and logit link for efficacy) with model terms to account for treatment, diagnostic group (PD, AD, MD), region (United States and non–United States), treatment-by-diagnostic group interaction, sex, baseline FTCD total score, and history of SUD (presence/absence). The analysis of safety is reported with observed NPSAE rates with confidence intervals, point estimates of NPSAE rates with confidence intervals from the model, and risk differences. Efficacy is reported utilizing observed abstinence rates and odds ratios. To address multiplicity concerns, pairwise treatment comparisons were restricted by psychiatric diagnosis (ie, a slice procedure) with a Tukey-based method for controlling family-wise error rate. Number needed to treat (NNT) was calculated as the inverse of the absolute risk reduction.

RESULTS

Four thousand fifty participants received at least 1 dose of study medication and were included in the safety cohort, whereas 4092 participants were randomized to study treatment and included in the efficacy cohort (see Consort Diagram, Supplemental Figure 1, Supplemental Digital Content 1, http://links.lww.com/JCP/A552; see Table 1 for baseline demographic, smoking-related, and psychiatric characteristics by primary psychiatric diagnostic group and treatment assignment). More than 90% in the MD subcohort had a lifetime diagnosis of MDD; the remainder had a bipolar disorder. Half of those with MDD met diagnostic criteria for recurrent MDD. More than 20% of the sample met diagnostic criteria for a prior SUD; more than 33% met *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* diagnostic criteria for a comorbid Axis I psychiatric illness, and more than 12% of participants reported a prior suicide attempt.

Neuropsychiatric Safety

Of 4050 participants in the safety cohort, 239 (5.9%) experienced at least 1 moderate or severe NPSAE in the prespecified, primary safety end point. The observed incidence of the primary NPSAE varied little across diagnostic by treatment groups (see Fig. 1 for observed rates of NPSAEs). In the statistical model of those reporting 1 or more NPSAE, there was no significant main effect of treatment, psychiatric diagnostic subgroup (PD, AD, or MD), region, or baseline FTCD total score and no treatment-by-psychiatric diagnostic group interaction. Female sex ($P = 0.0012$) and a prior SUD ($P < 0.0001$) were significantly associated with NPSAE occurrence. The point estimate for incidence of 1 or more moderate to severe NPSAEs during a smoking cessation attempt across treatment groups was 6.2 (1.6–10.8) on varenicline, 8.0 (3.3–12.8) on bupropion, 6.4 (2.3–10.5) on NRT, and 7.3 (2.8–11.8) on placebo in those with PD; 6.5 (3.3–9.6) on varenicline, 8.7 (4.9–12.5) on bupropion, 3.8 (0.8–6.8) on NRT, and 6.1 (2.9–9.3) on placebo for those with AD; and 7.7 (5.7–9.6) on varenicline, 6.9 (5.0–8.7) on bupropion, 6.8 (5.0–8.6) on NRT, and 5.9 (4.3–7.5) on placebo for those with MD (Table 2). Confidence intervals for the estimated difference in NPSAE rate between active treatments and placebo in the overall psychiatric cohort and within psychiatric diagnosis included zero for all comparisons.

Table 2 presents the observed incidence of the primary NPS end point, its 16 components, and Supplemental Table 1, Supplemental Digital Content 2, http://links.lww.com/JCP/A553, presents NPS events that were severe, that were serious adverse events (SAEs), or that led to treatment discontinuation, as well as suicidal ideation or behavior elicited by the C-SSRS. The observed rate of NPSAEs in the composite end point meeting criteria for an SAE, for example, life threatening, leading to hospitalization, was 1.4% overall, occurring in 55 of 4050 participants. The combined incidence of NPSAEs in the primary end point that were either SAEs, of severe intensity, or led to treatment

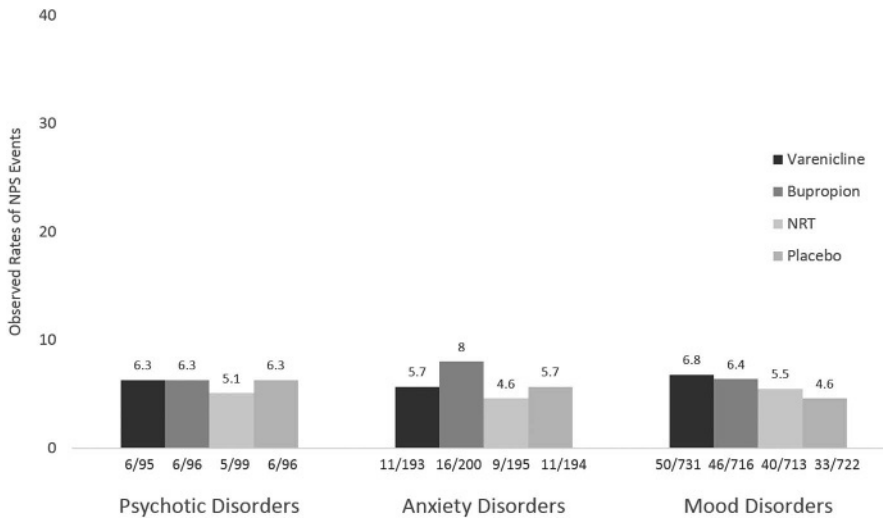


FIGURE 1. Participants with 1 or more observed NPSAE in the primary end point by diagnostic group. Period for ascertainment of NPSAEs is during 12-week treatment and 30-day follow-up.

TABLE 2. Incidence of the Primary Composite Neuropsychiatric End Point and Its Components

	PDs (n = 386)				ADs (n = 782)				MDs (n = 2882))			
	Varenicline (n = 95)	Bupropion (n = 96)	Nicotine Patch (n = 99)	Placebo (n = 96)	Varenicline (n = 193)	Bupropion (n = 200)	Nicotine Patch (n = 195)	Placebo (n = 194)	Varenicline (n = 731)	Bupropion (n = 716)	Nicotine Patch (n = 713)	Placebo (n = 722)
Observed incidence of the primary composite NPS end point	6 (6.3)	6 (6.3)	5 (5.1)	6 (6.3)	11 (5.7)	16 (8.0)	9 (4.6)	11 (5.7)	50 (6.8)	46 (6.4)	40 (5.6)	33 (4.6)
Estimated primary composite NPS end point, % (95% confidence interval)	6.2 (1.6–10.8)	8.0 (3.3–12.8)	6.4 (2.3–10.5)	7.3 (2.8–11.8)	6.5 (3.3–9.6)	8.7 (4.9–12.5)	3.8 (0.8–6.8)	6.1 (2.9–9.3)	7.7 (5.7–9.6)	6.9 (5.0–8.7)	6.8 (5.0–8.6)	5.9 (4.3–7.5)
Observed events—all components of primary composite NPS end point												
Anxiety	0	0	1 (1.0)	0	1 (0.5)	3 (1.5)	2 (1.0)	0	4 (0.5)	1 (0.1)	3 (0.4)	2 (0.3)
Depression	1 (1.1)	0	0	1 (1.0)	1 (0.5)	1 (0.5)	1 (0.5)	1 (0.5)	4 (0.5)	3 (0.4)	6 (0.8)	4 (0.6)
Feeling abnormal	0	0	0	0	0	0	0	0	0	1 (0.1)	0	0
Hostility	0	0	0	0	0	0	0	0	0	0	0	0
Agitation	2 (2.1)	2 (2.1)	1 (1.0)	1 (1.0)	4 (2.1)	7 (3.5)	2 (1.0)	5 (2.6)	19 (2.6)	20 (2.8)	18 (2.5)	16 (2.2)
Aggression	2 (2.1)	0	0	2 (2.1)	3 (1.6)	3 (1.5)	2 (1.0)	3 (1.5)	9 (1.2)	6 (0.8)	5 (0.7)	3 (0.4)
Delusions	1 (1.1)	0	1 (1.0)	0	0	0	0	0	0	1 (0.1)	0	0
Hallucinations	2 (2.1)	2 (2.1)	1 (1.0)	0	1 (0.5)	0	0	1 (0.5)	2 (0.3)	2 (0.3)	1 (0.1)	1 (0.1)
Homicidal ideation	0	0	0	0	0	0	0	0	0	0	0	0
Mania	0	1 (1.0)	0	1 (1.0)	1 (0.5)	0	1 (0.5)	1 (0.5)	6 (0.8)	8 (1.1)	2 (0.3)	4 (0.6)
Panic	0	1 (1.0)	1 (1.0)	0	1 (0.5)	6 (3.0)	3 (1.5)	2 (1.0)	6 (0.8)	9 (1.3)	9 (1.3)	5 (0.7)
Paranoia	1 (1.1)	0	0	1 (1.0)	0	0	0	0	0	0	0	1 (0.1)
Psychosis	1 (1.1)	1 (1.0)	2 (2.0)	1 (1.0)	0	0	1 (0.5)	0	3 (0.4)	1 (0.1)	0	0
Suicidal behavior	0	0	0	0	0	0	0	0	1 (0.1)	1 (0.1)	0	1 (0.1)
Suicidal ideation	0	1 (1.0)	1 (1.0)	0	2 (1.0)	1 (0.5)	1 (0.5)	0	3 (0.4)	0	2 (0.3)	2 (0.3)
Completed suicide	0	0	0	0	0	0	0	0	0	0	0	0

discontinuation was 2.2% overall and similar across diagnostic group and treatment assignment.

Broadening the list of NPSAEs beyond the predefined primary NPS end point to include mild AEs and any events captured through AE reporting and coded to the MedDRA Psychiatric Disorder and Disturbances System Organ Class, including sleep-related AEs, yielded observed overall rates of 21.5% (83/386) in the PD cohort, 41.4% (324/782) in the AD cohort, and 41.7% (1202/2882) in the MD cohort. These were most commonly abnormal dreams with varenicline and NRT, anxiety with bupropion and NRT, and insomnia with bupropion and NRT (Supplemental Table 2, Supplemental Digital Content 3, http://links.lww.com/JCP/A554).

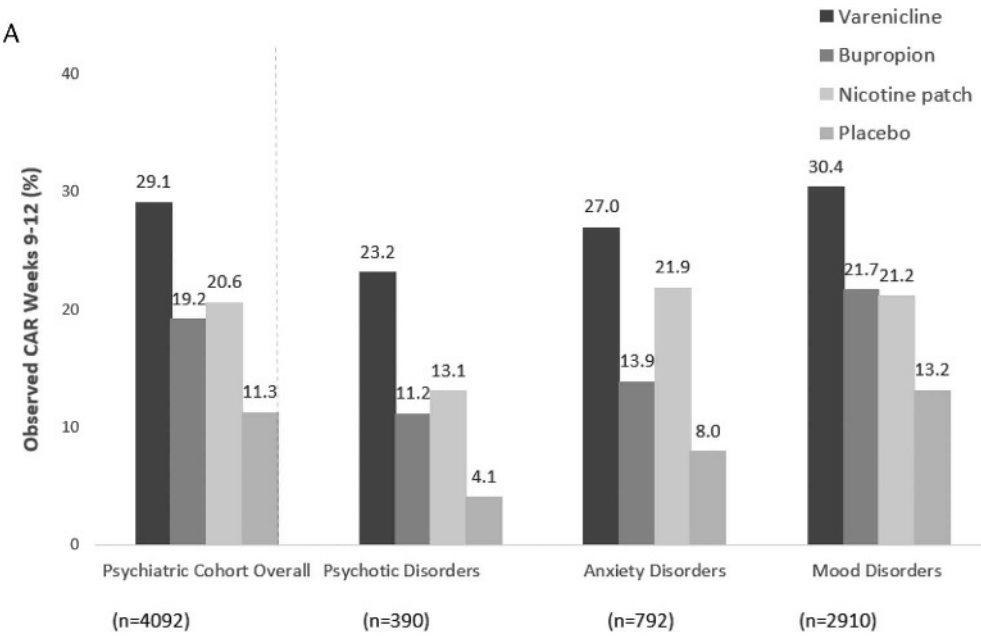
Additional Ratings of Anxiety, Depression, and Suicidal Ideation and Behavior

The rate of suicidal ideation and/or behavior on C-SSRS was similar across active treatments and placebo and less than 4% in each cohort (Supplemental Table 1, Supplemental Digital Content 2, http://links.lww.com/JCP/A553). Average weekly HADS anxiety and depression subscale scores decreased (improved) from baseline to end of treatment +30 days similarly across all treatment arms in each psychiatric cohort (Supplemental Figure 3, Supplemental Digital Content 4, http://links.lww.com/JCP/A555).

Treatment Efficacy for Continuous Abstinence

Of 4092 randomized participants, 820 achieved continuous abstinence for weeks 9 to 12 (9–12CA). Observed abstinence rates by treatment group in the psychiatric cohort and by diagnostic group are shown in Figure 2A. In the overall model for 9–12CA, there were significant effects of treatment ($P < 0.0001$), psychiatric diagnostic subgroup ($P < 0.0001$), region ($P < 0.0001$), and FTCD total score ($P < 0.0001$) and no significant treatment-by-psychiatric diagnosis interaction and no significant effect of sex or prior SUD. The odds ratios (95% confidence interval) for 9–12CA versus placebo in the overall psychiatric population were 4.57 (2.59–8.06) for varenicline, 2.22 (1.21–4.06) for bupropion, and 2.76 (1.53–4.97) for NRT patch. In within-diagnosis comparisons of treatment efficacy, the estimated odds ratios for 9–12CA for the active treatments versus placebo were greater than 3.0 for varenicline, greater than 1.9 for bupropion, and greater than 1.8 for NRT for all diagnostic groups; pairwise comparisons of treatment effects on 9–12CAR within diagnostic subgroups are provided in Figure 2B. The significant effect of

A



B

Treatment comparison	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Varenicline vs placebo	4.57 (2.59 to 8.06)	6.93 (1.61 to 29.84)	4.55 (2.05 to 10.11)	3.03 (2.13 to 4.32)
Bupropion vs placebo	2.22 (1.21 to 4.06)	2.99 (0.63 to 14.14)	1.91 (0.81 to 4.51)	1.91 (1.32 to 2.76)
Secondary comparisons				
Nicotine patch vs placebo	2.76 (1.53 to 4.97)	3.40 (0.74 to 15.61)	3.43 (1.52 to 7.74)	1.80 (1.24 to 2.61)
Varenicline vs nicotine patch	1.66 (1.11 to 2.49)	2.04 (0.75 to 5.55)	1.33 (0.72 to 2.46)	1.68 (1.23 to 2.32)
Bupropion vs nicotine patch	0.80 (0.51 to 1.27)	0.88 (0.28 to 2.73)	0.56 (0.28 to 1.12)	1.06 (0.76 to 1.48)
Varenicline vs bupropion	2.06 (1.35 to 3.17)	2.32 (0.82 to 6.58)	2.38 (1.21 to 4.69)	1.59 (1.16 to 2.18)

CAR, continuous abstinence rate; CI, confidence interval; OR, odds ratio

FIGURE 2. Comparison of continuous abstinence rates. A, Observed rates of continuous abstinence for study weeks 9 to 12. B, Comparison of odds of continuous abstinence for weeks 9 to 12 by treatment assignment and diagnostic group. From the GLIMMIX Procedure for Generalized Linear Mixed Models model that included terms for treatment, psychiatric diagnostic group, sex, Fagerstron Test for Cigarette Dependence total score, prior alcohol or substance use disorder, and region.

psychiatric diagnosis was such that those with an MD were more likely than those with a PD to achieve 9–12CA. Compared with placebo, NNT for 9–12CAR for varenicline was 6 for all disorders. Numbers needed to treat for bupropion were 12 for MD, 14 for PD, and 17 for AD. Numbers needed to treat for NRT were 8 for AD, 12 for PD, and 13 for MD.

There were significant effects of treatment, region, and severity of dependence on 9–24CAR, with no significant effect of psychiatric diagnosis, sex, and SUD and no treatment-by-psychiatric diagnosis interaction (see Supplemental Figure 2, Supplemental Digital Content 5, http://links.lww.com/JCP/A556, for pairwise comparisons of treatment effects on 9–24CAR within diagnostic subgroups). Compared with placebo, NNTs for week 9–24CAR for varenicline were 8 for PD and 11 for AD and MD. Numbers needed to treat for bupropion were 17 for PD, 18 for MD, and 26 for AD. Numbers needed to treat for NRT were 11 for AD, 17 for PD, and 29 for MD.

DISCUSSION

EAGLES is the largest randomized, placebo-controlled smoking cessation trial in smokers with PD, AD, or MDs and the first trial to allow evaluation of relative NPS safety and efficacy of first-line smoking cessation treatments and placebo in smokers with these psychiatric illnesses, who have higher smoking rates, lower cessation rates,[12] and a large and growing mortality disparity, for which tobacco smoking is considered to be the largest single contributor.[13,16]

Regarding NPS safety, we report no main effect of treatment, no main effect of diagnostic subcohort, and no treatment-by-diagnostic subcohort interaction on incidence of NPSAEs in a model that included region, sex, nicotine dependence severity, and prior SUD diagnosis. Female sex and prior SUD were associated with higher incidence of NPSAEs. The observed rate of NPSAEs in the primary outcome was 4.6% to 8.0%, similar across treatments within and between diagnostic groups. Thus, psychiatric diagnosis was not predictive of likelihood of experiencing a moderate to severe NPSAE, within the overall psychiatric cohort. Prior reports that female sex[41,42] and prior SUD[43] are associated with more severe nicotine withdrawal symptoms are consistent with our findings. Neuropsychiatric adverse events of mild intensity were fairly common; were similar across treatments, including placebo; and may represent expected events during a cessation attempt, independent of treatment. Importantly, no psychiatric subcohort or treatment by diagnostic subcohort category was identified as at particular risk of the most clinically worrisome NPSAEs, including hostility, aggression, severe depression, suicidal ideation, or suicidal behavior. Thus, we do not find evidence that primary PD, AD, or MD diagnosis should guide choice of pharmacotherapeutic cessation aids from an NPS safety stand point.

In interpreting the safety data, it is notable that, while participants were considered to be clinically stable with respect to their psychiatric illness at enrollment, they were also at risk of NPSAEs in this trial. They had, on average, moderate severity of nicotine dependence at baseline, putting them at risk of nicotine withdrawal symptoms during a cessation attempt. Many had significant baseline psychiatric symptoms, including hallucinations, delusions, and depressive symptoms revealed by baseline assessments, despite clinically determined best treatment for their psychiatric disorder. Half of those with MDD (90% of the MD subcohort) had recurrent MDD, and one-third met the diagnostic criteria for a comorbid psychiatric illness, including a prior SUD, factors associated with heavier smoking, more severe dependence, and fewer cessation attempts,[12,44,45] and 12% reported a suicide attempt in their lifetime. Thus, we conclude that these safety results are relevant in a broad range of clinical settings where smokers with PD, AD, and MD receive care and have the opportunity to be offered smoking cessation treatment, from mainstream physical health services to mental health settings.

Regarding efficacy, we previously reported a significant treatment effect on 9–12CAR and 9–24CAR, with varenicline superior to bupropion, NRT, and placebo, and bupropion and NRT superior to placebo, with no treatment-by-psychiatric cohort (vs nonpsychiatric cohort) interaction.[30] Here, we similarly report a significant main effect of treatment on abstinence within the psychiatric cohort and no treatment-by-diagnostic subgroup (PD, AD, or MD) interaction.

The major aim of this analysis was to provide guidance on clinical benefit-risk assessment of smoking cessation treatment choices for smokers with specific mental health conditions. This analysis demonstrates fairly common mild NPS symptoms, not different by treatment, and relatively rare serious NPSAEs ascertained with the NAEI, C-SSRS, and HADS, also not different by treatment, including placebo, or diagnostic group, whereas efficacy of all active treatments was demonstrated over placebo across all psychiatric diagnostic subgroups for 9–12CAR and 9–24CAR. Odds ratios for 9–12CAR for active treatments compared with placebo within diagnostic groups ranged from 1.8 for bupropion for those with ADs to 6.9 for varenicline for those with PDs. The results notably replicate consistent reports of very low abstinence rates of approximately 4% for smokers with PDs with behavioral treatment (and placebo) alone.[3] Low abstinence rates with behavioral treatment alone, combined with underutilization of effective smoking cessation pharmacotherapy,[13,22] may underlie the persistently high smoking rate and the growing mortality disparity, now estimated at more than 28 years in those with PDs.[16]

The efficacy effect estimates within diagnostic cohorts are consistent with the prior literature where such comparisons exist.[3,6,7] Varenicline was superior to placebo for week 9–12CAR and 9–24CAR for all diagnostic groups. In smokers with MDs, varenicline was significantly superior to bupropion and NRT, and varenicline, bupropion, and NRT were significantly superior to placebo. For those with ADs, varenicline was significantly superior to bupropion and placebo and nominally superior to NRT, whereas NRT was significantly superior to placebo, and bupropion was nominally superior to placebo. For smokers with psychotic illness, varenicline was significantly superior to placebo and nominally superior to bupropion and NRT patch, whereas bupropion and NRT patch were nominally superior to placebo. Although some corrected confidence intervals for odds ratios included 1 for the within-diagnosis analyses, the AD and PD subcohorts were not well powered for the comparisons; these did not change our conclusions based on the overall model and lack of significant treatment-by-diagnosis interaction.

An algorithm for clinical best practices is evolving for smoking cessation treatment in the general population, with varenicline and combination NRT having superior efficacy to single NRT and bupropion, all with superior efficacy to placebo.[46] While more work is needed, there is interest in developing guidelines for smoking cessation treatment for smokers with psychiatric illnesses.[3,47–49] This report should contribute to that effort with the first placebo-controlled efficacy data for NRT in smokers with PDs, for varenicline, bupropion, and NRT in those with many ADs, and for replicating findings from prior trials that smokers with PD, AD, and MDs can quit smoking with pharmacotherapeutic cessation aids with minimal effects on psychiatric symptoms.[7,49–51] These results, taken in the context of the larger sample, in which varenicline had superior efficacy to NRT and bupropion and all active treatments tested

were superior to placebo, with no treatment-by-diagnosis interaction, suggest that the relative effectiveness of smoking cessation therapies in the general population of smokers[46] applies for smokers with PD, AD, and MDs.

Limitations

This secondary analysis had limitations in addition to those reported for the overall trial.[30] Without a control group not attempting to quit smoking, conclusions cannot be drawn regarding whether the observed NPSAE rate is greater than baseline risk of adults with stable PD, AD, and MD. Dual NRT, considered first-line treatment,[46] was not tested. According to the a priori efficacy outcomes for the trial, the cutoff for biochemical verification of self-reported abstinence was CO 10 ppm or less, although this may not capture light smoking. Pairwise comparisons in some subgroups are likely underpowered. For instance, in the PD subcohort, the corrected confidence intervals for efficacy for two of the active treatments against placebo include an odds ratio of 1; however, the point estimates are greater than 2. In the psychiatric cohort as a whole, the group for which the study was powered, significant differences were observed for 9–12CAR and 9–24CAR for all active treatments versus placebo. Our ability to evaluate comorbid SUD as a moderator was limited to those with a prior SUD; thus, results may not extend to those with a current SUD.

CONCLUSIONS

In adults with PD, AD, and MDs, 12 weeks of treatment with varenicline, bupropion, and NRT were well tolerated during a smoking cessation attempt and comparable to placebo. The preponderance of evidence suggests that in smokers with these psychiatric illnesses, consistent with relative efficacy reported in the general population, varenicline is associated with higher rates of smoking cessation than NRT or bupropion, and all 3 active treatments are associated with superior abstinence rates to placebo.

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