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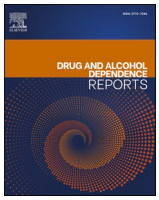

Sex effects in predictors of smoking abstinence and neuropsychiatric adverse events in the EAGLES trial☆

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HIGHLIGHTS

- There is limited information regarding sex effects on cessation-related neuropsychiatric adverse events or interactions with psychiatric status.
- We conducted a secondary analysis of data from EAGLES of 8144 participants randomized to varenicline, bupropion, nicotine patch or placebo to quit smoking.
- We found significant sex effects on neuropsychiatric adverse events and cessation outcomes.
- There were no significant interactions with psychiatric cohort and sex on cessation or adverse events.
- Findings did support prior work demonstrating relative increased efficacy of varenicline for women.

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ABSTRACT

Significance There are sex effects in abstinence outcomes across all smoking cessation medications, but there is limited information regarding sex effects on cessation-related neuropsychiatric adverse events (NPSAEs) or interactions with psychiatric status. METHODS: Secondary analysis of data from EAGLES of 8144 adults who smoke cigarettes randomized to varenicline, bupropion, nicotine patch or placebo. Design characteristics included region (within/outside US), psychiatric cohort (absent/present), and treatment. Baseline variables included demographics, smoking history, prior use of study treatments, lifetime suicide-related history, and prior psychiatric co-morbidities and medication use. Design characteristics were forced into logistic regressions models, and then interactions among sex, design elements, and baseline characteristics were evaluated for NPSAEs and 6-month cessation outcomes. RESULTS: Findings demonstrated a significant interaction of sex and race ($p < 0.02$); Black women were more likely to report NPSAEs than Black men. For cessation outcomes, there were no significant interactions with psychiatric cohort and sex. Women vs men with higher baseline levels of smoking had lower odds of continuous abstinence. Women vs men who used varenicline previously had lower odds of continuous abstinence. For 6-month point prevalence, sex interacted with baseline cigarettes per day ($p < 0.01$) similar to the interaction for continuous abstinence. Sex interacted with medication ($p < 0.03$), such that women vs men had relatively greater success at achieving point prevalence abstinence on varenicline. CONCLUSIONS: Overall, results demonstrated important sex and racial differences in the incidence of NPSAEs, but psychiatric status did not interact with sex on cessation outcomes. Findings did support prior work demonstrating relative increased efficacy of varenicline for women.

1. Introduction

Worldwide, 22% of the population uses tobacco leading to 8 million deaths per year (WHO, 2022). Women who smoke experience exacerbated health risks compared with men, including serious cardiovascular and lung disease (Ceribelli et al., 2007; Cote and Chapman, 2009;

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Huxley and Woodward, 2011; Kiyohara and Ohno, 2010; Tan et al., 2010). Moreover, findings indicate women experience greater health benefits from smoking cessation than their male counterparts (Mercuro et al., 2010; Rahmanian et al., 2011), yet women are less successful then men in quitting smoking (Perkins and Scott, 2008; Piper et al., 2010; Smith et al., 2016; Voci et al., 2021; Wetter et al., 1999). A comprehensive meta-analytic review, across efficacy trials, effectiveness trials, prospective observational studies, and cross-sectional studies, concluded that women were less likely to quit as compared to men (Smith et al., 2016).

Contributing to these disparities, some currently available treatments are not as effective for women. Nicotine replacement and bupropion are less effective for women, when compared to men (Aubin et al., 2004; Bohadana et al., 2003; Gonzales et al., 2002; Perkins and Scott, 2008; Scharf and Shiffman, 2004; Smith et al., 2017a, 2017b; Weinberger et al., 2014). Perkins and Scott (2008) found that transdermal nicotine was 40% more efficacious for men as compared to women at 6-months post quit attempt. In a review of 42 placebo-controlled trials, we found that 22 studies examined outcomes by sex and gender, and when men and women differed, women had poorer outcomes than men (Weinberger et al., 2014). Across the 42 studies, there was no available data by sex on medication compliance, adverse events, withdrawal, or craving. In a meta-analysis of 4421 adults who smoke cigarettes, Scharf and Shiffman (2004) found that bupropion equally increased rates of quitting in women (odds ratio = 2.47), and men (odds ratio = 2.53). However, rates of quitting overall were 21% lower in women, regardless of treatment condition.

Studies of sex differences in varenicline efficacy have found a preferential response for women who smoke. In a large meta-analytic investigation examining 10,641 adults who smoke, comprising 98% of all available Phase II and Phase III data examining varenicline vs placebo, quit rates in the placebo arms were lower in women, but absolute rates of quitting were equal across men and women. Thus, women had a larger relative response to varenicline, particularly for the short-term (46% more efficacious at the end of treatment) and intermediate (34% more efficacious at the 6-month follow up) outcomes. Varenicline was equally effective for women and men at the one-year follow-up (McKee et al., 2016). In a network meta-analysis to examine the relative efficacy of bupropion, nicotine replacement and varenicline, varenicline was found to be more efficacious than transdermal nicotine or bupropion for women, and that neither nicotine nor bupropion increased quitting in women (Smith et al., 2017a). For men, however, all three medications were found to be effective (odds ratio's > 1), but that there were no statistical differences between them (Smith et al., 2017a). These findings were replicated with Phase IV data from the Current Population Survey ($n = 7906$) comparing varenicline to transdermal nicotine patch (Smith et al., 2017b). For women, varenicline was superior to nicotine replacement, whereas for men, the efficacy of varenicline and transdermal nicotine did not differ.

While sex differences in medication efficacy exist, there is little information regarding potential factors which may underlie these differences or which may modify these differences, such as demographic characteristics, level of nicotine dependence, or psychiatric status. Across these variables, baseline sex and gender differences have been demonstrated. For example, sex differences in the relationship between nicotine dependence (Smith et al., 2014b) and psychiatric status (Smith et al., 2014a) have been demonstrated but is not known how sex might interact with these variables and medication, to predict cessation outcomes. Across studies examining sex differences in smoking cessation medication efficacy, there is also little information available regarding potential sex differences in adverse events, especially cessation-related neuropsychiatric adverse events (NPSAEs).

For the current study we conducted a secondary analysis of data from the Evaluating Adverse Events in a Global Smoking Cessation Study (EAGLES; NCT01456936) (Anthenelli et al., 2016) trial to identify sex differences in medication efficacy and adverse events. The EAGLES study was an international study, which recruited participants from 140 centers in 16 countries across 5 continents. The EAGLES trial provided a unique data source that was sufficiently powered ($n = 8144$) and designed (i.e., psychiatric status was a primary design variable) to examine interactions of baseline variables including demographics, smoking history, prior use of study treatments, lifetime suicide-related history, with gender, psychiatric status, and treatment (varenicline, bupropion, nicotine patch, placebo) on NPSAEs and cessation outcomes. While there is limited literature on which to base specific hypothesis, we did hypothesize that psychiatric status may interact with female sex to reduce medication efficacy.

2. Methods

2.1. Design

We conducted a secondary analysis of data from EAGLES in 8144 participants randomized to varenicline (1 mg twice daily), bupropion (150 mg twice daily), nicotine patch (21 mg per day) or placebo for 12 weeks; 8058 received 1 dose or more of treatment and were then followed for up to 24-weeks. Study procedures and consent were approved by institutional review boards for participating sites (see Anthenelli et al., 2016 for full trial design and procedural details). Consolidated Standards of Reporting Trials (CONSORT) diagram, separating study flow by psychiatric status and gender is presented in Fig. 1.

2.2. Participants

Participants in EAGLES were recruited from 16 countries between November 2011 and January 2015. Eligibility criteria included smoking 10 or more cigarettes per day, 18 to 75 years of age, and with or without pre-specified current or lifetime psychiatric diagnosis (including meeting diagnostic criteria for psychotic, anxiety, mood, and borderline personality disorders (American Psychiatric Association, 2000).

2.3. Measures

2.3.1. Design variables

Design variables included one randomization variable (treatment [varenicline, bupropion, nicotine transdermal replacement (NTR) or placebo]) and two stratification-based variables (psychiatric cohort [yes/no] and region [US, non-US]).

2.3.2. Variable of interest

Biological/birth sex (male, female) was collected during the screening visit. Gender was not assessed.

2.3.3. Baseline variables

Baseline variables included basic demographic and body habitus characteristics including race, weight, body mass index (BMI). Smoking characteristics included nicotine dependence (Fagerstrom Test for Cigarette Dependence [FTCD] Score (Fagerström, 2012), age of smoking initiation (years), cigarettes per day over the past 30 days, duration of smoking (years), number of quit attempts, whether participant lives with a smoker (yes/no), whether participant has contact with a smoker (yes/no) and has had at least one quit attempt (yes/no). Prior use of study treatments included prior use of varenicline (yes/no), bupropion (yes/no), and nicotine replacement therapy (yes/no). Depression and anxiety symptoms were assessed with the Hospital Anxiety and Depression Scale (anxiety score, depression score; (Zigmond and Snaith, 1983). Aggression was assessed with the Buss-Perry Aggression Questionnaire (BPAQ; Buss and Perry, 1992). Lifetime history of self-harm was assessed with the Columbia Suicide Severity Scale (C-SSRS; (Posner et al., 2011). Additional baseline variables included psychiatric medication use (yes/no), psychotropic medication use (yes/no), co-morbid diagnosis (yes/no), and lifetime alcohol or substance use

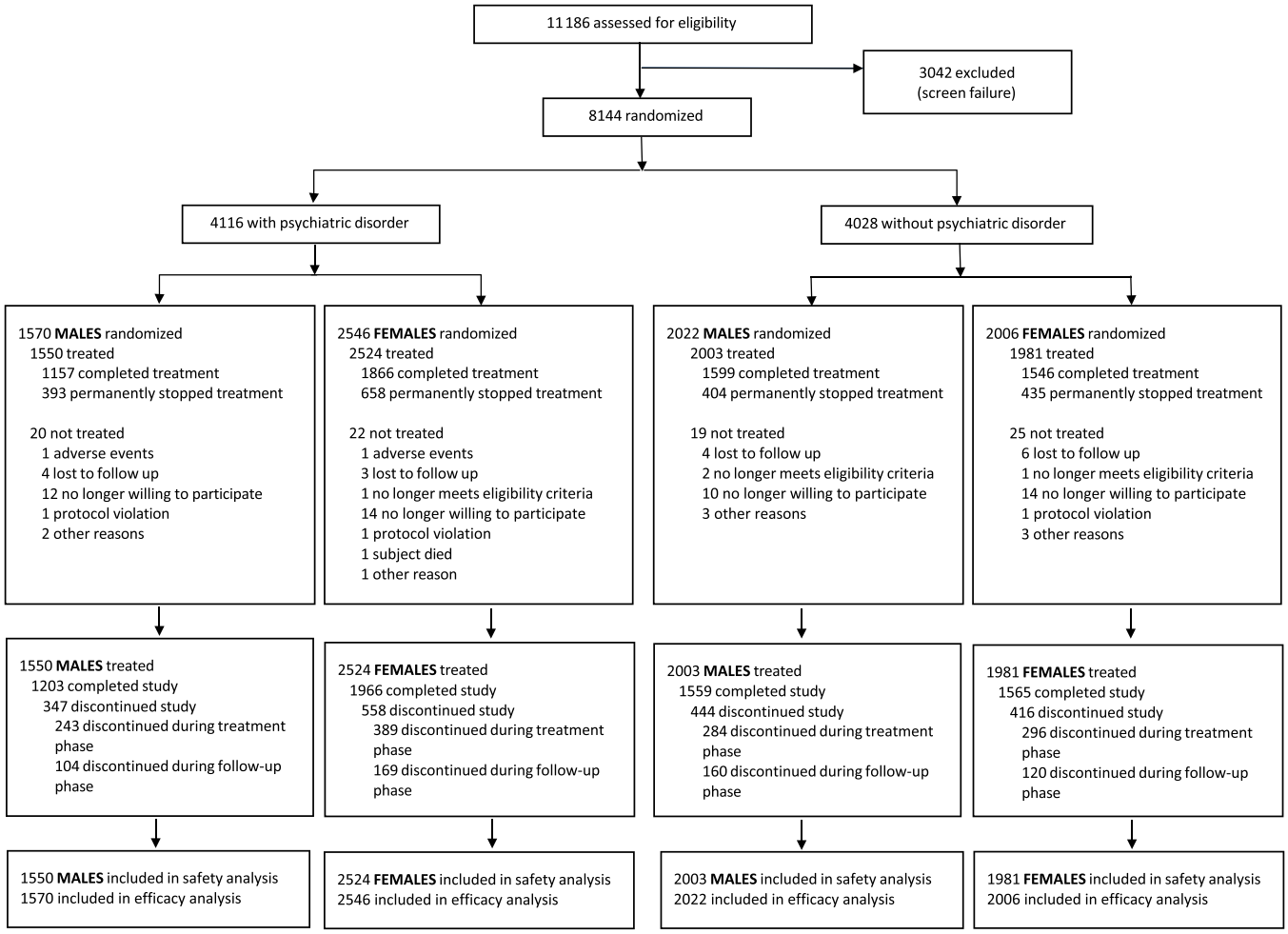

Fig. 1. CONSORT flow diagram.

disorder diagnosis.

2.3.4. Outcome variables

2.3.4.1. Adverse events. NPSAEs is a treatment-emergent composite of 16 neuropsychiatric symptom categories (anxiety, depression, feeling abnormal, hostility, agitation, aggression, delusions, hallucinations, homicidal ideation, mania, panic, paranoia, psychosis, suicidal ideation, suicidal behavior or completed suicide). As described previously (Anthenelli et al., 2016), in order to be included in the composite primary safety outcome, the four more commonly reported NPSAE clusters (anxiety, depression, feeling abnormal and hostility), needed to be rated at the severe level indicating that the participant's functioning was substantially affected by that complaint. The other 12 symptom categories could be rated as moderate (some interference with daily functioning) or severe (substantial interference with daily functioning). Treatment emergent adverse events (AE) includes all-causality adverse events reported by at least 5% of participants in any treatment group.

2.3.4.2. Smoking outcomes. Smoking outcomes included Continuous Abstinence, defined as abstinence from week 9 to 24 (CA 9–24), and Point-Prevalence Abstinence at Week 24 (PPA 24). Abstinence was defined as no self-reported cigarette use through the specified period in addition to exhaled carbon monoxide concentration less than 10 ppm.

2.4. Statistical analyses

Statistical analyses were performed using SAS® Version 9.4 (SAS Institute Inc, 2013). Baseline descriptive summaries were presented for all randomized subjects by sex, treatment, and cohort. Sex comparisons in baseline variables were (1) performed individually without any multiplicity protection, (2) based on general linear modeling (continuous case) or logistic modeling (discrete case; logit or glogit link as warranted) controlling for treatment and cohort, and (3) presented in a suggestive context rather than as formal hypothesis testing.

Efficacy analyses were based on all randomized subjects while safety analyses were based on all randomized and treated subjects. Observed counts and percentages of endpoints were tabulated by sex, cohort, and treatment. Abstinence endpoints conservatively considered missing data as non-abstinent, while adverse events followed a treatment-emergent paradigm of last dose plus 30 days.

The potential effect of sex on smoking abstinence (CA 9–24 and PPA 24) and NPSAE endpoints was examined via backward-selection logistic regression analyses. In each case, the design variables – treatment, cohort, and region were forced inclusions into the statistical model. Other candidate terms included (1) sex and demographic/baseline variables as main effects (see list in Table 1), (2) two-way interaction of sex with each candidate demographic/baseline variable, (3) two-way interaction of treatment with each candidate demographic/baseline variable, (4) two-way interaction of cohort with each candidate demographic/baseline variable, and (5) the sex by treatment by cohort interaction. The stay criterion was set to 5%. The backward selection was structured to allow non-significant main effects underpinning

Table 1
Baseline characteristics: all randomized participants.

	Males[a]								Females[a]							
	All (*N* = 3592)	Non-psychiatric cohort (*N* = 2022)				Psychiatric cohort (*N* = 1570)				All (*n* = 4552)	Non-psychiatric cohort (*N* = 2006)				Psychiatric cohort (*N* = 2546)			
		VAR *n* = 517	BUP *n* = 508	NRT *n* = 503	PBO *n* = 494	VAR *n* = 397	BUP *n* = 395	NRT *n* = 387	PBO *n* = 391		VAR *n* = 488	BUP *n* = 493	NRT *n* = 510	PBO *n* = 515	VAR *n* = 635	BUP *n* = 638	NRT *n* = 638	PBO *n* = 635
Baseline characteristic																		
Race																		
White	2921 (81.3)	427 (82.6)	424 (83.5)	419 (83.3)	401 (81.2)	327 (82.4)	312 (79.0)	299 (77.3)	312 (79.8)	3728 (81.9)	401 (82.2)	406 (82.4)	421 (82.5)	425 (82.5)	528 (83.1)	518 (81.2)	509 (79.8)	520 (81.9)
Black	519 (14.4)	75 (14.5)	59 (11.6)	61 (12.1)	63 (12.8)	58 (14.6)	70 (17.7)	70 (18.1)	63 (16.1)	643 (14.1)	64 (13.1)	59 (12.0)	69 (13.5)	64 (12.4)	87 (13.7)	97 (15.2)	110 (17.2)	93 (14.6)
Other/unknown	152 (4.2)	15 (2.9)	25 (4.9)	23 (4.6)	30 (6.1)	12 (3.0)	13 (3.3)	18 (4.7)	16 (4.1)	181 (4.0)	23 (4.7)	28 (5.7)	20 (3.9)	26 (5.0)	20 (3.1)	23 (3.6)	19 (3.0)	21 (3.3)
Age (years)[b]	45.7 (12.8)	45.7 (13.4)	45.7 (13.6)	45.2 (13.4)	44.7 (13.1)	46.1 (12.2)	45.9 (12.3)	46.8 (11.7)	46.1 (11.5)	47.1 (12.0)	45.9 (12.4)	46.3 (12.4)	46.9 (12.1)	47.0 (12.4)	47.9 (11.4)	46.9 (12.3)	48.1 (11.4)	47.4 (11.5)
Weight (kg)[b]	88.5 (18.8)	86.7 (18.8)	86.8 (19.1)	87.4 (17.5)	87.6 (16.9)	91.5 (19.8)	91.0 (20.3)	88.9 (18.4)	89.6 (19.8)	75.9 (19.8)	73.1 (17.7)	73.9 (19.0)	75.7 (20.0)	74.0 (19.1)	77.7 (20.7)	77.2 (20.0)	75.8 (19.4)	78.5 (21.0)
BMI (kg/m^2)	28.0 (5.5)	27.5 (5.7)	27.6 (5.6)	27.6 (5.5)	27.9 (4.9)	28.8 (5.5)	28.8 (6.0)	28.1 (5.4)	28.5 (5.8)	28.2 (7.0)	27.3 (6.3)	27.6 (6.8)	28.0 (7.0)	27.6 (6.8)	28.8 (7.4)	28.6 (6.9)	28.2 (6.8)	28.9 (7.3)
Smoking characteristics																		
FTND score[b]	5.8 (2.0)	5.5 (2.0)	5.6 (2.0)	5.5 (2.0)	5.6 (2.0)	6.1 (1.9)	6.2 (2.0)	6.1 (2.0)	6.1 (2.1)	5.7 (2.0)	5.5 (2.0)	5.4 (2.0)	5.6 (1.9)	5.5 (2.0)	6.0 (2.0)	6.0 (1.9)	5.9 (1.9)	5.8 (2.0)
Age started smoking (years)[b]	17.1 (4.9)	16.9 (4.2)	17.1 (4.7)	17.2 (4.7)	17.0 (4.5)	16.9 (4.7)	17.2 (5.6)	17.4 (6.1)	16.8 (4.6)	17.4 (5.3)	17.4 (4.8)	17.3 (4.6)	17.2 (4.7)	17.2 (4.3)	17.1 (5.2)	17.5 (6.2)	17.4 (5.3)	17.8 (6.3)
Cigarettes smoked per day in last month[b]	21.9 (8.8)	22.0 (9.0)	21.9 (8.6)	21.6 (8.5)	21.2 (8.1)	22.1 (8.6)	22.2 (8.9)	22.4 (10.3)	22.4 (8.8)	19.7 (7.6)	19.4 (7.2)	19.4 (6.8)	20.0 (7.9)	19.8 (7.6)	19.7 (7.5)	19.6 (7.6)	19.8 (8.1)	19.7 (7.7)
Duration of smoking (years)[b]	27.9 (12.9)	28.0 (13.4)	28.0 (14.0)	27.2 (13.4)	27.3 (13.0)	28.2 (12.2)	27.7 (12.6)	28.6 (12.4)	28.5 (11.6)	28.7 (11.9)	27.7 (12.1)	28.4 (11.9)	29.1 (12.1)	29.0 (12.1)	29.3 (11.6)	28.4 (12.3)	29.1 (11.5)	28.2 (11.7)
Number of quit attempts	3.5 (11.8)	3.7 (18.9)	3.4 (13.8)	3.4 (6.2)	3.1 (7.6)	3.7 (10.9)	3.0 (4.3)	3.5 (5.3)	4.4 (16.5)	3.5 (5.5)	2.8 (3.3)	3.2 (4.2)	3.0 (3.8)	3.2 (7.2)	3.2 (4.7)	3.8 (8.1)	3.2 (5.2)	3.2 (4.7)
Lives with a smoker[b]	1189 (33.1)	192 (37.1)	170 (33.5)	170 (33.8)	162 (32.8)	117 (29.5)	126 (31.9)	108 (27.9)	144 (36.8)	1742 (38.3)	193 (39.5)	209 (42.4)	216 (42.4)	200 (38.8)	231 (36.4)	222 (34.8)	248 (38.9)	223 (35.1)
Contact with a smoker[b]	2632 (73.3)	385 (74.5)	390 (76.8)	376 (74.8)	365 (73.9)	290 (73.0)	272 (68.9)	279 (72.1)	275 (70.3)	3054 (67.1)	326 (66.8)	333 (67.5)	345 (67.6)	376 (73.0)	438 (69.0)	427 (66.9)	398 (62.4)	411 (64.7)
At least one previous quit attempt[b]	2932 (81.4)	404 (78.1)	409 (80.5)	418 (83.1)	382 (77.3)	327 (82.4)	323 (81.8)	325 (84.0)	335 (85.7)	3804 (83.6)	418 (85.7)	409 (83.0)	421 (82.5)	423 (82.1)	534 (84.1)	534 (83.7)	535 (83.9)	530 (83.5)
Varenicline[b]	506 (14.1)	66 (12.8)	63 (12.4)	76 (15.1)	60 (12.1)	53 (13.4)	66 (16.7)	60 (15.5)	62 (15.9)	765 (16.8)	66 (13.5)	85 (17.2)	83 (16.3)	79 (15.3)	101 (15.9)	134 (21.0)	112 (17.6)	105 (16.5)
Bupropion[b]	304 (8.5)	38 (7.4)	44 (8.7)	44 (8.7)	37 (7.5)	33 (8.3)	40 (10.1)	31 (8.0)	37 (9.5)	540 (11.9)	57 (11.7)	49 (9.9)	50 (9.8)	54 (10.5)	83 (13.1)	88 (13.8)	81 (12.7)	78 (12.3)
NRT[b]	869 (24.2)	110 (21.3)	125 (24.6)	108 (21.5)	111 (22.5)	102 (25.7)	103 (26.1)	107 (27.6)	103 (26.3)	1267 (27.8)	119 (24.4)	135 (27.4)	150 (29.4)	140 (27.2)	194 (30.6)	176 (27.6)	180 (28.2)	173 (27.2)
HADS																		
Total score[b]	5.9 (5.6)	4.1 (4.2)	4.1 (4.2)	4.0 (4.1)	4.4 (4.5)	7.7 (6.1)	8.5 (6.8)	8.2 (6.4)	8.3 (6.0)	6.7 (6.1)	4.6 (4.6)	4.1 (4.0)	4.4 (4.1)	4.6 (4.2)	8.6 (6.6)	8.9 (7.0)	8.5 (6.7)	8.2 (6.4)
Anxiety subscale score[b]	3.6 (3.4)	2.5 (2.6)	2.6 (2.6)	2.6 (2.6)	2.7 (2.7)	4.6 (3.6)	5.0 (4.1)	4.9 (3.9)	5.2 (3.8)	4.3 (3.6)	3.1 (3.0)	2.8 (2.7)	2.9 (2.6)	3.0 (2.8)	5.4 (3.9)	5.5 (4.0)	5.3 (4.0)	5.1 (3.7)
Depression subscale score	2.3 (2.8)	1.6 (2.2)	1.6 (2.1)	1.5 (2.0)	1.7 (2.2)	3.1 (3.1)	3.5 (3.4)	3.3 (3.2)	3.1 (2.9)	2.4 (3.0)	1.5 (2.1)	1.3 (1.9)	1.5 (2.0)	1.6 (2.0)	3.2 (3.4)	3.4 (3.6)	3.2 (3.3)	3.1 (3.3)
Aggression Q total score[b]	56.5 (17.3)	53.9 (15.7)	53.6 (15.3)	53.6 (15.0)	53.7 (15.9)	58.7 (18.4)	59.5 (18.8)	60.7 (19.1)	61.1 (19.0)	54.7 (17.4)	50.7 (15.1)	50.1 (15.1)	50.8 (16.0)	50.9 (14.7)	56.5 (18.1)	58.1 (18.7)	59.7 (19.0)	57.4 (17.6)

(*continued on next page*)

Table 1 (*continued*)

	All (*N* = 3592)	Males[a]						Females[a]					
		Non-psychiatric cohort (*N* = 2022)			Psychiatric cohort (*N* = 1570)			Non-psychiatric cohort (*N* = 2006)			Psychiatric cohort (*N* = 2546)		
		VAR *n* = 517	BUP *n* = 508	NRT *n* = 503	PBO *n* = 494	VAR *n* = 397	BUP *n* = 395	NRT *n* = 387	PBO *n* = 391	All (*n* = 4552)	VAR *n* = 488	BUP *n* = 493	NRT *n* = 510	PBO *n* = 515	VAR *n* = 635	BUP *n* = 638	NRT *n* = 638	PBO *n* = 635
C-SRRS BEID[b]	591 (16.5)	15 (2.9)	23 (4.5)	22 (4.4)	20 (4.0)	117 (29.5)	135 (34.2)	121 (31.3)	138 (35.3)	1032 (22.7)	34 (7.0)	21 (4.3)	30 (5.9)	29 (5.6)	238 (37.5)	234 (36.7)	220 (34.5)	226 (35.6)
Ideation[b]	580 (16.1)	15 (2.9)	22 (4.3)	21 (4.2)	20 (4.0)	112 (28.2)	135 (34.2)	120 (31.0)	135 (34.5)	1001 (22.0)	33 (6.8)	21 (4.3)	29 (5.7)	29 (5.6)	228 (35.9)	228 (35.7)	214 (33.5)	219 (34.5)
Behavior[b]	190 (5.3)	2 (0.4)	3 (0.6)	4 (0.8)	2 (0.4)	44 (11.1)	47 (11.9)	39 (10.1)	49 (12.5)	360 (7.9)	4 (0.8)	6 (1.2)	3 (0.6)	4 (0.8)	93 (14.6)	99 (15.5)	73 (11.4)	78 (12.3)
Psychiatric medication use[b]	961 (26.8)	26 (5.0)	28 (5.5)	26 (5.2)	29 (5.9)	224 (56.4)	205 (51.9)	210 (54.3)	213 (54.5)	1668 (36.6)	58 (11.9)	53 (10.8)	63 (12.4)	73 (14.2)	382 (60.2)	345 (54.1)	353 (55.3)	341 (53.7)
Psychotropic medication use[b]	819 (22.8)	23 (4.4)	26 (5.1)	24 (4.8)	27 (5.5)	191 (48.1)	167 (42.3)	177 (45.7)	184 (47.1)	1506 (33.1)	52 (10.7)	47 (9.5)	61 (12.0)	69 (13.4)	343 (54.0)	304 (47.6)	314 (49.2)	316 (49.8)
Comorbid diagnosis[b]	647 (18.0)	4 (0.8)	4 (0.8)	0	3 (0.6)	157 (39.5)	153 (38.7)	158 (40.8)	168 (43.0)	864 (19.0)	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)	199 (31.3)	225 (35.3)	232 (36.4)	204 (32.1)
Alcohol/substance dependence/use[b]	482 (13.4)	3 (0.6)	3 (0.6)	0	2 (0.4)	117 (29.5)	108 (27.3)	118 (30.5)	131 (33.5)	475 (10.4)	0	0	0	0	110 (17.3)	133 (20.8)	119 (18.7)	113 (17.8)

Data are mean (SD), or n (%).

[a] All randomized population.

[b] Denotes significant difference between sex ($p < 0.05$).

BEID, behavior and ideation; BUP, bupropion; BMI, Body Mass Index; C-SSRS, Columbia-Suicide Severity Rating Scale; FTND, Fagerström Test for Nicotine Dependence; HADS, Hospital Anxiety and Depression Scale; NRT, nicotine replacement therapy; PBO, placebo; VAR, varenicline.

significant interactions to remain in the model. The strategy was to consider the analysis in the context of a secondary, post-hoc analysis with a specific interest in sex. Thus, sex interactions should be considered for hypothesis generating purposes but foregoing higher-level interactions to be more parsimonious in exploratory model building while also acknowledging that sex was not a design variable and, as such, not necessarily balanced enough to combat spurious confounding situations. In each case, Akaike Information Criterion (AIC) was used to assess the benefit of the final backward selection model relative to a basic design model and to a sex-infused design model. See Supplementary Tables 2–4 for full model results.

3. Results

All baseline characteristics, with the exception of race, number of prior quit attempts and depression scores, significantly differed by sex ($p < 0.05$; see Table 1). At baseline, weight, BMI, FTCD scores, CPD, contact with a smoker, aggression scores, rates of co-morbid diagnosis, and rates of alcohol and substance use dependence were higher in men, otherwise all other baseline sex differences were greater for women. NPSAEs and AEs were tabulated by design characteristics (see Table 2 and Supplementary Materials).

Backward-selection logistic regression models for NPSAEs demonstrated significant main effects of design characteristics (cohort, region, sex) but not treatment. Baseline variables demonstrating significant main effects on NPSAEs included: anxiety symptoms, baseline suicidal ideation/behavior, age, race, psychotropic medication, prior use of bupropion, lifetime alcohol or substance use diagnosis, and aggression scores. There were significant interactions between sex and region (Wald=5.55, $p < 0.02$), and sex and race (Wald=7.97, $p < 0.02$). Treatment-emergent NPSAEs were more prevalent in non-US women, Black women, and women of 'other' racial categories than men in the corresponding region and racial categories (see Fig. 2).

Backward-selection logistic regression models for CA 9–24 demonstrated significant main effects of design characteristics (treatment, region) but not cohort or sex. Baseline variables demonstrating significant main effects on CA 9–24 included: FTCD, CPD, age, BMI, race, prior use of NRT, and contact with smoker. There were significant interactions between sex and CPD (Wald=5.06, $p < 0.03$), and sex and prior use of varenicline (Wald=4.53, $p < 0.03$). Women had less success at achieving continuous abstinence if baseline smoking was more than 20 cigarettes per day. Women had less success at achieving continuous abstinence if they had previously used varenicline (see Fig. 3).

Backward-selection logistic regression models for PPA 24 demonstrated significant main effects of design characteristics (treatment, region, sex) but not cohort. Baseline variables demonstrating significant main effects on PPA 24 included: FTCD, CPD, age, BMI, anxiety symptoms, baseline suicidal ideation/behavior, age, race, psychotropic medication, prior use of NRT, age of smoking initiation, and contact with a smoker. There were significant interactions between sex and treatment (Wald=9.44, $p < 0.03$), and sex and CPD (Wald=7.51, $p < 0.01$). Varenicline-treated women had relatively greater success at achieving 7-day point prevalent abstinence at week 24 than men. Heavier smoking (>20 cigarettes per day) women had less success at achieving 7-day point prevalence abstinence at week 24 compared to heavier smoking men (see Fig. 4).

4. Discussion

This secondary analysis of data from the EAGLES trial uniquely demonstrated significant interactions between baseline variables and sex on NPSAEs and cessation outcomes. Treatment emergent NPSAEs were more prevalent in non-US women, Black women, and women of 'other' racial categories vs men in the corresponding region and racial categories. We found interactions of sex with prior use of varenicline and baseline cigarette use with cessation outcomes. Prior use of varenicline

Table 2
Participants With Observed Treatment-Emergent Neuropsychiatric Adverse Events.

	Males								Females							
	Non-psychiatric cohort				Psychiatric cohort				Non-psychiatric cohort				Psychiatric cohort			
	VAR *n* = 510	BUP *n* = 504	NRT *n* = 499	PBO *n* = 490	VAR *n* = 392	BUP *n* = 388	NRT *n* = 384	PBO *n* = 386	VAR *n* = 480	BUP *n* = 485	NRT *n* = 507	PBO *n* = 509	VAR *n* = 634	BUP *n* = 629	NRT *n* = 632	PBO *n* = 629
NO	502 (98.4)	495 (98.2)	487 (97.6)	476 (97.1)	370 (94.4)	373 (96.1)	367 (95.6)	369 (95.6)	475 (99.0)	472 (97.3)	494 (97.4)	499 (98.0)	589 (92.9)	576 (91.6)	595 (94.1)	596 (94.8)
YES	8 (1.6)	9 (1.8)	12 (2.4)	14 (2.9)	22 (5.6)	15 (3.9)	17 (4.4)	17 (4.4)	5 (1.0)	13 (2.7)	13 (2.6)	10 (2.0)	45 (7.1)	53 (8.4)	37 (5.9)	33 (5.2)

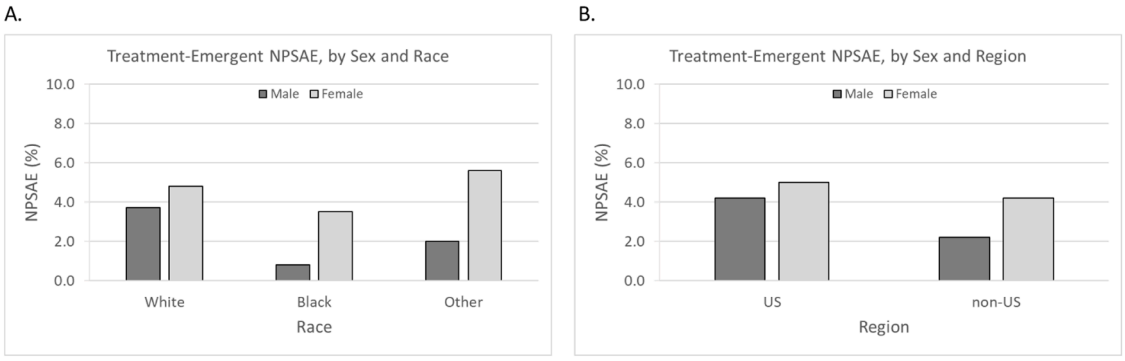

Fig. 2. Treatment emergent Neuropsychiatric Side Effects (NPSAE)s by Gender and Race (A); by Gender and Region (B).

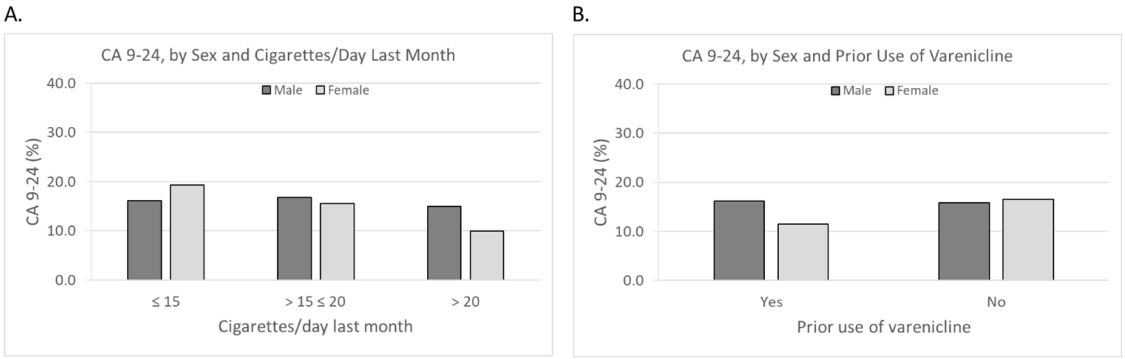

Fig. 3. CA 9–24 by Gender and Cigarettes per Day (CPD) (A); by Gender and Prior Use of Varenicline (B).

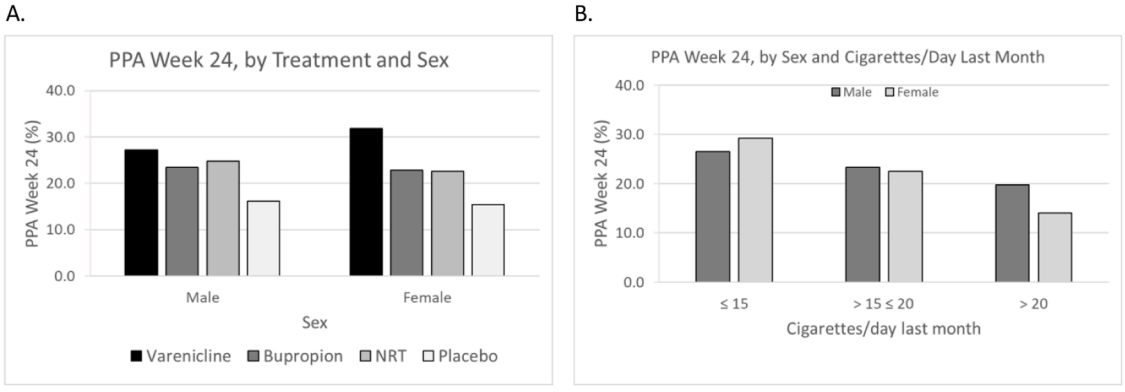

Fig. 4. Point Prevalence Abstinence (PPA) 24 By Gender and Treatment (A); by Gender and Cigarettes per Day (CPD) (B).

and heavier baseline cigarette use predicted poorer cessation outcomes for women as compared to men. Also, women treated with varenicline had improved cessation outcomes than men treated with varenicline. Overall, we found no significant interactions between sex with psychiatric status and any of the baseline variables, in predicting cessation outcomes or NPSAEs.

All of the baseline variables assessed in the EAGLES trial, with the exception of race, prior quit attempts and depression scores, demonstrated significant sex differences at the start of the trial. Prior secondary analysis of the EAGLES trial data had examined sex as a covariate in treatment effects but had not considered baseline sex differences in their analysis (West et al., 2018). This fact highlights the need to assess for these substantial differences, and to account for these sex differences in analysis when attempting to determine whether sex impacted on important study-related outcomes. In the case of the EAGLES trial, baseline variables which demonstrated sex differences, interacted with sex in predicting both NPSAEs as well as cessation outcomes.

Importantly, we found that sex interacted with race when examining rates of NPSAEs. Black women versus Black men had greater rates of NPSAEs, as did women versus men of 'other' racial categories, and women versus men is non-US regions. White women and White men did not differ in their rates. Prior secondary analysis of the EAGLES trial data demonstrated main effects in sex and race. Females had greater rates of NPSAEs than males (Anthenelli et al., 2019), and adults who identified as Black had lower rates of moderate-to-severe NPSAEs than adults who identified as White (Nollen et al., 2021). Our results indicate that sex and race interact, and that this difference is driven by higher rates in non-White women. Such findings highlight the importance of intersectional analysis, that sex and racial identities can work on multiple levels to impact on health outcomes. A recent meta-analysis spanning several systems identified that sex differences in pharmacokinetics may underlie why women might experience greater medication-related adverse events (Zucker and Prendergast, 2020). However, explanations for sex and race differences in NPSAEs associated with smoking cessation would be speculative and requires further research.

Heavier levels of baseline smoking (>20 cigarettes per day) predicted worse smoking cessation outcomes for both point prevalence abstinence, as well as continuous abstinence at the 6-month timepoint for women compared with men at similar levels of baseline smoking. This finding was independent of psychiatric status or treatment condition. Women have greater rates of return to smoking following smoking cessation treatment (Smith et al., 2016), baseline smoking is associated with return to smoking (Yong et al., 2013), and this effect may be particularly pronounced in women who have heavier cigarette use.

Prior use of varenicline was associated with lowered rates of continuous abstinence for women, versus men who had previously used varenicline. In a study examining the efficacy of re-treatment with varenicline (at least one prior failed smoking cessation attempt with varenicline), the authors report no sex differences in rates of smoking cessation (Gonzales et al., 2014). Information about why varenicline was discontinued (e.g., adverse events, return to smoking) was not examined in the current study, nor the Gonzales et al. (2014) study. In the Gonzales et al. (2014) study, participants were required to have previously taken varenicline for a two-week period, whereas the EAGLES trial queried about prior varenicline use with a yes/no option. It is possible that the Gonzales et al. (2014) study selected out those with initial negative adverse reactions to varenicline. However, prior use of varenicline in the EAGLES trial was not associated with increased NPSAEs (Anthenelli et al., 2019) but may be possibly related to increased non-psychiatric adverse events.

Varenicline-treated women had relatively greater success at achieving point-prevalence abstinence at 6 months than did men treated with varenicline. This finding supports prior work, demonstrating that varenicline had relatively greater efficacy for women, particularly for shorter-term outcomes (McKee et al., 2016; Smith et al., 2017a, 2017b). One possible explanation for this finding is based on nicotine metabolism. Women are known to metabolize nicotine more quickly from their systems than men, as assessed by the nicotine metabolite ratio (3′-hydroxycotinine:cotinine), and this effect is partially mediated by estrogen (Chenoweth et al., 2014). It has been found that women, due to faster metabolism, have a preferred therapeutic response to varenicline (Glatard et al., 2017). Additional translational research to understand how sex-sensitive mechanisms interact with medication efficacy are important to pursue.

Finally, psychiatric status did not interact with sex and baseline variables for NPSAEs or abstinence outcomes. This was surprising as there is evidence to indicate that women have greater associations between particular psychiatric disorders (e.g., depression, alcohol use disorder, PTSD) and smoking behavior (Smith et al., 2014a, 2020). The presence of psychiatric conditions has been one factor identified to explain why women may have more difficulty quitting. However, the EAGLES trial data demonstrated that treatments were equally effective for those with psychiatric conditions (Evins et al., 2019), with our findings demonstrating no sex interactions with this main effect.

Limitations with the EAGLES trial have been described previously (Anthenelli et al., 2016) and will not be recounted here. However, regarding the present secondary analysis, while psychiatric status was retained in the final models, information regarding psychiatric history, treatment, and severity variables were not available in the data, and these variables may interact with sex on smoking cessation outcomes and adverse events. The use of backward stepwise model selection can potentially result in false positives and that aspect should be considered a limitation when interpreting the fitted model. As an alternative, future research may consider a machine learning approach to identify sex-stratified predictors of treatment responses and adverse events. Imputing missing smoking status outcomes to smoking does have a general limitation in that it can potentially ignore effects arising from differences in subject disposition (such as discontinuation either of treatment or from study). The absence of a gender assessment in the EAGLEs trial is a limitation, and we acknowledge that medication effects and adverse events are likely a combination of both sex and gender effects (McKee and McRae-Clark, 2022).

In conclusion, this secondary analysis of the EAGLES trial data demonstrated that baseline sex differences existed for basic demographics, smoking history, prior use of study treatments, lifetime suicide-related history, anxiety and depression scores, aggression scores, prior use of study treatments, concurrent medications, co-morbid diagnosis, and lifetime alcohol and substance dependence. Future work examining sex differences in adverse events and smoking cessation outcomes needs to consider possible interactions with significant baseline differences. Overall, we found important racial differences in the incidence of NPSAEs for women and men. We also determined that psychiatric status did not interact with sex on cessation outcomes or NPSAEs. Findings did support prior work demonstrating relative increased efficacy of varenicline for women.

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Supplementary materials

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