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Research paper

Safety and efficacy of first-line smoking cessation pharmacotherapies in bipolar disorders: Subgroup analysis of a randomized clinical trial

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CA, continuous abstinence
CAR, continuous abstinence rate
PPA, point prevalence abstinence
NPC, nonpsychiatric cohort
NPSAE, neuropsychiatric adverse event

ABSTRACT

Objectives: Post hoc analyses of EAGLES data to examine safety and efficacy of first-line smoking cessation pharmacotherapies in smokers with bipolar disorders (BD).
Methods: Smokers with BD I/II (n = 285; 81.4% with BD I) and a comparison nonpsychiatric cohort (NPC; n = 2794) were randomly assigned to varenicline, bupropion, nicotine replacement therapy (NRT), or placebo for 12 weeks, plus weekly counseling. Primary outcomes were occurrence of moderate to severe neuropsychiatric adverse events (NPSAEs) and Weeks 9–12 biochemically-confirmed continuous abstinence (CA) rates.
Results: For BD smokers, NPSAE risk differences versus placebo were: varenicline, 6.17 (95% CI: –7.84 to 20.18); bupropion, 4.09 (–8.82 to 16.99); NRT, –0.56 (–12.34 to 11.22). ORs for Weeks 9–12 CA, comparing active medication to placebo among BD smokers were: varenicline, 2.61 (0.68–9.95); bupropion, 1.29 (0.31–5.37), NRT, 0.71 (0.14–3.74). Pooling across treatments, NPSAE occurrence was higher (10.7% versus 2.3%; $P < 0.001$) and CA rates were lower (22.8% versus 13.3%; $P = 0.008$) in BD than NPC.
Limitations: Study not powered to detect differences in safety and efficacy in the BD subcohort; generalizability limited to stably treated BD without current substance use disorders.
Conclusions: Smokers with BD had higher risk of NPSAEs and were less likely to quit overall than NPC smokers. Among smokers with BD, NPSAE risk difference estimates for active treatments versus placebo ranged from 1% lower to 6% higher. Efficacy of varenicline in smokers with BD was similar to EAGLES main outcomes; bupropion and NRT effect sizes were descriptively lower. Varenicline may be a tolerable and effective cessation treatment for smokers with BD.
Trial registration: ClinicalTrials.gov identifier (https://clinicaltrials.gov/): NCT01456936.

1. Introduction

The prevalence of smoking among individuals with bipolar disorders (BD) is two to three times higher than among individuals without psychiatric disorders (Heffner et al., 2011; Lasser et al., 2000) and, among the major psychiatric disorders, is second only to schizophrenia (Diaz et al., 2009; Dickerson et al., 2013). Quit rates among smokers with BD are 60% lower than in those with no psychiatric disorder (Lasser et al., 2000). Smokers with BD remain one of the most under-researched tobacco-related health disparities populations (George et al., 2012; Heffner et al., 2011).

Smokers with BD are excluded from most cessation trials, thus there are numerous gaps in the literature regarding the safety and efficacy of the first-line pharmacotherapies in these individuals. There have been only eight published prospective studies to date focusing on tobacco treatment for smokers with BD in an outpatient setting—two on development of a targeted behavioral treatment (Heffner et al., 2013, 2015); four focusing on pharmacotherapies for cessation (three on varenicline (Chengappa et al., 2014; Frye et al., 2013; Wu et al., 2012) and one on bupropion (Weinberger et al., 2008)); one focusing on

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extended use of varenicline for relapse prevention (Evins et al., 2014); and one focusing on abstinence-contingent monetary incentives and intensive behavioral interventions to accompany pharmacotherapy (Brunette et al., 2018). Six of these eight studies included < 20 participants with BD, making the findings inconclusive. In the largest pharmacotherapy trial to date ($n = 60$), Chengappa et al. (Chengappa et al., 2014) found a significant effect of varenicline on 7-day point prevalence abstinence (PPA) at the end of the 12-week treatment period, but not at the 6-month follow-up. Although underpowered to evaluate safety events, the trial found no statistically significant differences between treatment groups in mood rating scale scores but observed a trend toward higher incidence of depressed mood as an adverse event (AE) in the varenicline group.

To date, there have been no placebo-controlled trials of nicotine replacement therapy (NRT) for smokers with BD, only very small trials of bupropion (Weinberger et al., 2008), and no trials with multiple active pharmacotherapy arms to test comparative safety or efficacy. Additionally, conclusions about lower quit rates among smokers with BD are based on epidemiological data owing to the lack of prospective cessation studies, and it is unclear how quit rates compare to smokers without psychiatric disorders because quit rates in epidemiological studies can be influenced by differences in motivation to quit or treatment utilization. Finally, although previous evidence suggests that smokers with psychiatric disorders experience greater severity of nicotine withdrawal symptoms during quit attempts (Breslau et al., 1992), the comparative incidence of clinically significant psychiatric AEs (e.g., suicidal ideation or behavior, severe depression) that go beyond the affective disturbances observed in typical nicotine withdrawal is another important unknown.

These knowledge gaps are a major impediment to addressing the high rates of smoking among people with BD. Concerns about safety and effectiveness of medications for smoking cessation reduce clinicians' likelihood of offering these options, which are a critical part of the tobacco treatment armamentarium. To address these gaps, the first aim of these post-hoc exploratory analyses was to evaluate the comparative safety and efficacy of varenicline, bupropion, NRT (nicotine patch), and placebo for smokers with BD when provided along with behavioral counseling. The second aim was to compare rates of clinically significant neuropsychiatric AEs (NPSAEs) and cessation in smokers with BD compared with a country-matched cohort of smokers without psychiatric disorders.

2. Materials and methods

2.1. Participants

The sample ($n = 285$ with BD; $n = 2794$ without psychiatric disorders; eFigure 1 in the **Supplement**) was a subset of participants in EAGLES (Evaluating Adverse Events in a Global Smoking Cessation Study). Eligibility criteria have been previously described (Anthenelli et al., 2016) but, of relevance to this analysis, participants with BD were nested within the broader group of smokers with primary mood disorders (American Psychiatric Association, 2000). Participants in the BD subcohort, similar to the larger psychiatric cohort, had to be clinically stable, with no significant worsening of psychiatric status in the prior 6 months, no changes in treatment over the last 3 months, and no treatment changes planned during the period of study participation. Potential participants deemed to be at high risk of self-harm or suicidal behavior at screening were excluded. In addition to their primary diagnosis, participants could have had a history of other psychiatric diagnoses. However, substance use disorders within the past year were excluded owing to the potentially destabilizing effects of recent or current problem substance use. We included in the BD subcohort in this analysis those participants who met *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (DSM-IV-TR) criteria for either BD I or II as a primary diagnosis ($n = 281$) or as a comorbid psychiatric condition ($n = 4$) (American Psychiatric Association, 2000). The enrollment of subjects with BD was not allowed in EAGLES at sites in the EU (Bulgaria, Denmark, Finland, Germany, Slovakia, Spain) owing to a contraindication for bupropion in these subjects per local prescribing information. The nonpsychiatric cohort (NPC) included in this analysis is a country-matched subset of the larger cohort in EAGLES ($n = 4028$) based on countries where the regulatory agencies have not contraindicated bupropion in BD (i.e., Argentina, Australia, Brazil, Canada, Chile, Mexico, New Zealand, Russia, South Africa, USA).

2.2. Procedures

EAGLES (NCT01456936; https://clinicaltrials.gov) was a multinational study designed to assess the risk of clinically significant NPSAEs in smokers with ($n = 4074$) and without ($n = 3984$) psychiatric disorders treated with varenicline, bupropion, NRT, or placebo. A full description of EAGLES methodology is published (Anthenelli et al., 2016). EAGLES was reviewed and approved by each site's institutional review board or ethics committee and was conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent. Screening for participation included confirmation of psychiatric diagnoses using the Structured Clinical Interview for DSM-IV-TR (SCID) Axis I and II disorders (First et al., 1997, November 2002).

Randomization of eligible participants was computer generated and stratified by primary psychiatric disorder (none, mood, anxiety, psychotic, borderline personality) and region (US, Eastern Europe, Western Europe and other countries, South and Central America). Randomization was not stratified by diagnosis of BD within the mood disorder subcohort, nor was the study powered for evaluations of safety and efficacy in the BD subcohort. Treatment involved double-blind, triple-dummy administration of varenicline (1 mg twice daily), bupropion sustained release (150 mg twice daily), NRT (21 mg daily with tapering), or placebo. All participants received weekly brief (≤ 10 min) smoking cessation counseling based on Agency for Healthcare Research and Quality Guidelines (Fiore et al., 2008) (e.g., setting a quit date, managing withdrawal and cravings, etc.), with no counseling for mental health-related issues. The target quit date was 1 week after randomization, to coincide with the end of the titration period for varenicline and bupropion and the initiation of the NRT treatment. The treatment period was 12 weeks, with a 12-week follow-up phase.

Severity of nicotine dependence was assessed at baseline using the Fagerström Test for Cigarette Dependence (FTCD) (Fagerström, 2012). Psychiatric symptoms were assessed at baseline with the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983), the Columbia Suicide Severity Rating Scale (C-SSRS) (Posner et al., 2011), and the Buss-Perry Aggression Questionnaire (BPAQ) (Buss and Perry, 1992), and at all subsequent visits with HADS and C-SSRS. The primary outcome of clinically significant NPSAEs was based on AEs reported through unstructured (open-ended questions, direct observation, unsolicited collateral informant reports from family members or healthcare providers) and structured (Neuropsychiatric Adverse Events Interview [NAEI], review of C-SSRS and HADS data) methods. The primary outcome of cigarette smoking was assessed weekly using questionnaires on participants' use of tobacco and other nicotine products and verified biochemically by expired-air CO measurements. CO levels > 10 ppm were considered indicative of smoking (Benowitz et al., 2002). Adherence to cessation pharmacotherapies was assessed via self-report and corroborated through count of unused pills and patches that were brought to each study visit during the treatment period.

The primary safety endpoint was the occurrence of ≥1 moderate to severe NPSAE (regardless of the investigators' determination of treatment relatedness) fitting one of the prespecified 16 categories of events: anxiety, depression, feeling abnormal, hostility, agitation, aggression, delusions, hallucinations, homicidal ideation, mania, panic, paranoia, psychosis, suicidal behavior, suicidal ideation, or completed suicide. To

be considered an NPSAE, some had to be of at least a moderate severity (some interference with daily functioning): agitation, aggression, delusions, hallucinations, homicidal ideation, mania, panic, paranoia, psychosis, suicidal behavior, suicidal ideation, or completed suicide. Others had to be severe (substantial interference with daily functioning): anxiety, depression, feeling abnormal, and hostility. These operational definitions were prespecified in the analytic plan for EAGLES. Secondary NPSAE outcomes included psychiatric AEs of severe intensity only, NPSAEs resulting in treatment discontinuation, and psychiatric symptom scales. Exploratory NPSAE analyses focused on psychiatric AEs of any severity.

The primary efficacy endpoint was CO-confirmed continuous abstinence (CA) during the final 4 weeks of the treatment period (Weeks 9–12). Participants who were lost to follow-up or who missed the Week 12 visit were coded as smokers (West et al., 2005). Missing data for Weeks 9–11 were imputed using the backward carry method, and missing CO levels among self-reported nonsmokers were imputed as ≤ 10 ppm. Sensitivity analyses conducted in the larger trial indicated that imputed CO levels did not affect results. The secondary cessation outcome was CO-confirmed CA for Weeks 9–24. We also explored 7-day PPA at Weeks 12 and 24, which was a pre-specified secondary endpoint in the parent protocol.

2.3. Statistical analysis

Generalized linear models were used to test significance of the effects of treatment group, psychiatric cohort, and their interaction on moderate to severe NPSAEs and biochemically confirmed CA at end of treatment (Weeks 9–12) and through follow-up (Weeks 9–24). NPSAE outcomes are reported for the sample of randomized participants that took ≥ 1 dose of study medication (BD subcohort, $n = 280$; NPC, $n = 2761$), whereas smoking abstinence outcomes are reported for all randomized participants (BD subcohort, $n = 285$; NPC, $n = 2794$). In addition to the effects of interest, models included a term for region (US versus non-US). More granular location variables (i.e., study site) could not be incorporated in this subcohort analysis because they prevented model convergence. We adjusted all models for demographics (age, gender, race, BMI, weight), smoking (FTCD, start age, duration of smoking, cigarettes per day smoked in the past month, number of quit attempts, number with ≥1 quit attempt), and prior use of study medications (varenicline, bupropion, NRT) that were associated with NPSAE or efficacy outcomes using a forward stepwise method of selecting covariates. Analyses were conducted using SAS version 9 (SAS Institute Inc., Cary, NC, USA). All tests were two-tailed with $P < 0.05$ for statistical significance. A Tukey-Kramer adjustment was used to control for multiple comparisons within models. Because subgroup analyses are underpowered to answer the safety and efficacy research questions of the larger EAGLES trial, we prioritized effect size estimates and confidence intervals over statistical significance in our interpretation of the safety and efficacy data for the four treatment arms in the BD subcohort.

3. Results

Table 1 displays baseline participant characteristics. Within the BD subcohort, a substantially higher number of participants met criteria for BD I ($n = 232$; 81.4%) than BD II ($n = 53$). There were no significant differences in smoking heaviness or age by cohort ($P > 0.05$). However, smokers with BD had higher body mass index (BMI; $P < 0.001$), nicotine dependence severity (FTCD; $P < 0.001$), anxiety (HADS Anxiety; $P < 0.001$), depression (HADS Depression; $P < 0.001$), and aggression scale scores (BPAQ; $P < 0.001$). In addition, they were more likely to be female ($P = 0.015$), non-White ($P < 0.001$), taking a psychotropic medication ($P < 0.001$), to have comorbid psychiatric ($P < 0.001$) or a history of alcohol use disorders ($P < 0.001$), and to have had prior suicidal ideation and/or behavior ($P < 0.001$).

3.1. Medication adherence

For randomized participants who took ≥ 1 dose of study medication (BD subcohort, $n = 280$; NPC, $n = 2761$), the median duration of study drug exposure was 85.0 days (range, 83.5–85.0) across treatments and cohorts.

3.2. NPSAEs

As shown in Fig. 1, NPSAE incidence for BD smokers was: varenicline, 14.7%; bupropion, 11.9%; NRT, 6.3%; placebo, 8.8%. NPSAE risk differences versus placebo were: varenicline, 6.17 (95% CI: –7.84 to 20.18); bupropion, 4.09 (–8.82 to 16.99); and NRT, –0.56 (–12.34 to 11.22). In the model for NPSAE primary endpoint occurrence, there was no significant main effect of treatment and no treatment-by-cohort interaction, indicating that risk of NPSAEs did not differ by treatment group in either cohort. There was a main effect of cohort, with a higher overall incidence of NPSAEs in the BD subcohort versus the NPC (10.7% versus 2.3%; risk difference [RD], 7.73; 95% CI: 4.15 to 11.31). As shown in Table 2, the components in the NPSAE endpoint reported in ≥1% of the BD subcohort were: mania (more broadly operationalized as worsening of BD symptoms, including depression: $n = 13$; 4.6%); agitation ($n = 10$; 3.6%); and panic ($n = 3$; 1.1%). Notably, occurrence of mania symptoms among participants who received either varenicline (6.7%) or bupropion (6.0%) in the BD subcohort was very similar to those who received placebo (5.3%). The rates of permanent treatment discontinuations following moderate to severe NPSAEs in the primary endpoint (i.e., due to the investigators' belief that the medication might be contributing to the onset or maintenance of the event) in the BD subcohort were similar: varenicline (7%), bupropion (8%), NRT (2%), and placebo (5%) (Table 2). Suicidal ideation and/or behavior that met the criteria for the composite outcome of moderate to severe NPSAEs was infrequent, occurring among only one participant in the BD subcohort (in the varenicline group) and five participants in the NPC ($n = 2$ in the NRT group, and $n = 3$ in the placebo group).

Compared with the occurrence of the primary prespecified NPSAE endpoint, the incidence of *any* type of AE in the broad psychiatric disorders and disturbances category in Medical Dictionary for Regulatory Activities (MedDRA; including sleep-related AEs like insomnia) of any severity (ranging from mild to severe) descriptively differed across cohorts and treatments (BD subcohort, 36.8%; NPC, 30.9%; eTable 1 in the **Supplement**). By treatment group, rates for BD and NPC were: varenicline, 45% and 33.9%; bupropion, 44% and 32.4%; NRT, 25% and 30.3%; and placebo, 28% and 26.9%. The most common category of AEs was sleep disorders and disturbances (BD, 18.2%; NPC, 20.4%).

Across cohorts and treatments, HADS Anxiety and Depression subscale scores decreased or remained stable over time (Fig. 2).

3.3. Smoking abstinence

Weeks 9–12 CARs for BD smokers were: varenicline, 22.7%; bupropion, 11.6%; NRT, 7.7%; placebo, 10.2%. Odds ratios (ORs) for active treatments versus placebo were: varenicline, 2.61 (95% CI: 0.68 to 9.95); bupropion, 1.29 (95% CI: 0.31 to 5.37); and NRT, 0.71 (95% CI: 0.14 to 3.74) (Fig. 3). The model showed significant main effects of treatment group ($P < 0.001$) and cohort ($P = 0.03$) and no significant treatment-by-cohort interaction ($P = 0.026$). Across combined cohorts, varenicline was superior to bupropion (OR, 1.93; 95% CI: 1.07 to 3.48; $P = 0.005$), NRT (OR, 2.45; 95% CI: 1.18 to 5.06; $P = 0.002$), and placebo (OR, 3.36; 95% CI: 1.68 to 6.74; $P < 0.001$). None of the other pairwise differences between treatments were statistically significant. Although the treatment-by-cohort interaction was not statistically significant, the effect size estimates for active versus placebo comparisons within the NPC showed ORs of 4.33 for varenicline, 2.36 for bupropion, and 2.65 for NRT, which were descriptively higher than the BD

Table 1
Baseline characteristics of all randomized participants by treatment group and cohort.

	Bipolar disorders subcohort (N = 285)					Nonpsychiatric cohort[a] (N = 2794)				
	All (n = 285)	Varenicline (n = 75)	Bupropion (n = 86)	NRT (n = 65)	Placebo (n = 59)	All (n = 2794)	Varenicline (n = 692)	Bupropion (n = 688)	NRT (n = 711)	Placebo (n = 703)
Demographic characteristics										
Female sex,[b] n (%)	**166 (58.2)**	46 (61.3)	54 (62.8)	36 (55.4)	30 (50.8)	**1412 (50.5)**	344 (49.7)	350 (50.9)	359 (50.5)	359 (51.1)
Age, years, mean (SD)	**45.2 (11.9)**	43.8 (12.4)	45.0 (12.4)	45.9 (11.4)	46.4 (11.1)	**45.7 (13.2)**	45.4 (13.2)	45.8 (13.5)	46.1 (13.0)	45.5 (13.1)
Race,[b] n (%)										
White	**185 (64.9)**	53 (70.7)	54 (62.8)	38 (58.5)	40 (67.8)	**2097 (75.1)**	516 (74.6)	519 (75.4)	541 (76.1)	521 (74.1)
Black	**83 (29.1)**	18 (24.0)	26 (30.2)	22 (33.8)	17 (28.8)	**514 (18.4)**	139 (20.1)	118 (17.2)	130 (18.3)	127 (18.1)
Other	**17 (6.0)**	4 (5.3)	6 (7.0)	5 (7.7)	2 (3.4)	**183 (6.5)**	37 (5.3)	51 (7.4)	40 (5.6)	55 (7.8)
Region,[b] n (%)										
US	**254 (89.1)**	62 (82.7)	78 (90.7)	61 (93.8)	53 (89.9)	**1901 (68.0)**	473 (68.4)	472 (68.6)	480 (67.5)	476 (67.7)
Non-US[c]	**31 (10.9)**	13 (17.3)	8 (9.3)	4 (6.2)	6 (10.2)	**893 (32.0)**	219 (31.6)	216 (31.4)	231 (32.5)	227 (32.3)
BMI, kg/m^2,[b] mean (SD)	**30.6 (6.9)**	31.4 (7.1)	30.1 (7.3)	29.9 (6.2)	30.8 (7.0)	**28.4 (6.5)**	28.2 (6.5)	28.3 (6.6)	28.6 (6.7)	28.5 (6.3)
Smoking characteristics										
FTCD score,[b] mean (SD)	**6.6 (1.7)**	6.8 (1.6)	6.7 (1.7)	6.3 (1.8)	6.6 (1.6)	**5.4 (2.0)**	5.4 (2.0)	5.4 (2.1)	5.4 (1.9)	5.4 (2.0)
Duration of smoking, years, mean (SD)	**27.0 (12.6)**	26.4 (13.6)	26.7 (13.2)	26.4 (11.9)	28.9 (11.3)	**27.8 (13.2)**	27.4 (13.2)	28.0 (13.4)	28.1 (13.2)	27.7 (12.9)
Cigarettes smoked per day in past month, n, mean (SD)	**20.4 (8.2)**	20.6 (7.7)	21.6 (9.2)	18.6 (6.9)	20.1 (8.5)	**20.1 (8.2)**	20.4 (8.6)	20.1 (8.0)	20.1 (8.1)	19.9 (7.9)
Previous quit attempts, n, mean (SD)	**3.3 (7.3)**	2.4 (3.6)	3.5 (3.9)	3.4 (4.7)	4.2 (13.9)	**3.3 (8.3)**	3.1 (6.5)	3.5 (12.0)	3.3 (5.5)	3.3 (7.7)
Prior use of study treatments										
Varenicline, n (%)	**39 (13.7)**	7 (9.3)	15 (17.4)	7 (10.8)	10 (16.9)	**461 (16.5)**	108 (15.6)	114 (16.6)	131 (18.4)	108 (15.4)
Bupropion,[d] n (%)	**33 (11.6)**	6 (8.0)	8 (9.3)	11 (16.9)	8 (13.6)	**317 (11.3)**	80 (11.6)	78 (11.3)	80 (11.3)	79 (11.2)
NRT, n (%)	**72 (25.3)**	12 (16.0)	25 (29.1)	14 (21.5)	21 (35.6)	**762 (27.3)**	170 (24.6)	193 (28.1)	207 (29.1)	192 (27.3)
Psychiatric characteristics										
Primary psychiatric diagnosis, n (%)										
Bipolar I[e]	**228 (80.0)**	60 (80.0)	71 (82.6)	47 (72.3)	50 (84.7)	**NA**	NA	NA	NA	NA
Bipolar II	**53 (18.6)**	14 (18.7)	13 (15.1)	18 (27.7)	8 (13.6)	**NA**	NA	NA	NA	NA
Any comorbid Axis I diagnosis,[b] n (%)	**164 (57.5)**	49 (65.3)	39 (45.3)	41 (63.1)	35 (59.3)	**11 (0.4)**	5 (0.7)	2 (0.3)	0 (0.0)	4 (0.6)
Personality disorder	**21 (7.4)**	8 (10.7)	6 (7.0)	2 (3.1)	5 (8.5)	**2 (0.1)**	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)
Anxiety disorder	**51 (17.9)**	12 (16.0)	13 (15.1)	14 (21.5)	12 (20.3)	**3 (0.1)**	1 (0.1)	1 (0.1)	0 (0.0)	1 (0.1)
Other	**25 (8.8)**	10 (13.3)	5 (5.8)	7 (10.8)	3 (5.1)	**0 (0.0)**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Substance use disorder history,[b] n (%)	**118 (41.4)**	33 (44.0)	28 (32.6)	31 (47.7)	26 (44.1)	**6 (0.2)**	3 (0.4)	1 (0.1)	0 (0.0)	2 (0.3)
Alcohol use disorder history	**84 (29.5)**	22 (29.3)	18 (20.9)	21 (32.3)	23 (39.0)	**4 (0.1)**	2 (0.3)	0 (0.0)	0 (0.0)	2 (0.3)
Lifetime suicide-related history from C-SSRS,[b] n (%)	**129 (45.3)**	38 (50.7)	32 (38.1)	27 (42.2)	30 (52.6)	**169 (6.0)**	46 (6.8)	38 (5.6)	44 (6.2)	41 (5.9)
Suicidal ideation	**122 (42.8)**	35 (46.7)	32 (38.1)	26 (40.6)	29 (50.9)	**166 (5.9)**	45 (6.6)	37 (5.4)	43 (6.1)	41 (5.9)
Suicidal behavior	**72 (25.3)**	26 (34.7)	11 (13.1)	17 (26.6)	18 (31.6)	**20 (0.7)**	5 (0.7)	7 (1.0)	4 (0.6)	4 (0.6)
HADS score, mean (SD)										
Anxiety subscale score[b]	**6.0 (4.6)**	5.9 (4.1)	5.7 (5.0)	6.8 (4.6)	5.9 (4.3)	**3.0 (2.8)**	3.1 (2.9)	2.9 (2.8)	2.8 (2.7)	3.1 (2.8)
Depression subscale score[b]	**3.8 (3.8)**	3.8 (3.6)	3.9 (4.3)	4.1 (3.7)	3.6 (3.5)	**1.6 (2.1)**	1.7 (2.2)	1.6 (2.1)	1.5 (2.0)	1.7 (2.1)
BPAQ score,[b] mean (SD)	**65.6 (23.4)**	64.5 (24.0)	64.1 (24.6)	70.7 (22.8)	63.7 (21.0)	**52.2 (16.0)**	52.7 (16.2)	52.3 (16.0)	51.4 (15.6)	52.3 (16.1)
Receiving any psychotropic medication at enrollment,[b] n (%)	**202 (72.1)**	54 (72.0)	54 (64.3)	48 (75.0)	46 (80.7)	**295 (10.7)**	66 (9.7)	68 (10.0)	76 (10.7)	85 (12.2)
Antidepressants	**123 (43.9)**	34 (45.3)	36 (42.9)	24 (37.5)	29 (50.9)	**97 (3.5)**	20 (2.9)	19 (2.8)	23 (3.3)	35 (5.0)
Anxiolytics, hypnotics, and other sedatives	**69 (24.6)**	19 (25.3)	15 (17.9)	25 (39.1)	10 (17.5)	**204 (7.4)**	47 (6.9)	47 (6.9)	57 (8.1)	53 (7.6)
Antipsychotics	**129 (46.1)**	35 (46.7)	38 (45.2)	30 (46.9)	26 (45.6)	**13 (0.5)**	2 (0.3)	2 (0.3)	2 (0.3)	7 (1.0)
Mood stabilizers	**38 (13.6)**	7 (9.3)	12 (14.3)	9 (14.1)	10 (17.5)	**15 (0.5)**	5 (0.7)	1 (0.1)	1 (0.1)	8 (1.2)
Other[f]	**2 (0.7)**	0 (0.0)	2 (2.4)	0 (0.0)	0 (0.0)	**4 (0.1)**	1 (0.1)	1 (0.1)	2 (0.3)	0 (0.0)

BMI, body mass index; BPAQ, Buss-Perry Aggression Questionnaire; C-SSRS, Columbia Suicide Severity Rating Scale; FTCD, Fagerström Test for Cigarette Dependence; HADS, Hospital Anxiety and Depression Scale; NA, not applicable; NRT, nicotine replacement therapy (transdermal nicotine patch); SD, standard deviation.

[a] This nonpsychiatric cohort is a country-matched population, i.e., it excludes participants from Bulgaria, Denmark, Finland, Germany, Slovakia, and Spain, where subjects with bipolar disorder I/II were not enrolled.

[b] $P < 0.05$ for comparison of baseline variable by cohort.

[c] Argentina, Australia, Brazil, Canada, Chile, Mexico, New Zealand, Russia, and South Africa.

[d] Bupropion prior use for smoking cessation or other indications.

[e] Four participants in the bipolar disorders subcohort had bipolar I as secondary diagnosis.

[f] Psychostimulants, amino acids, and herbals or botanicals.

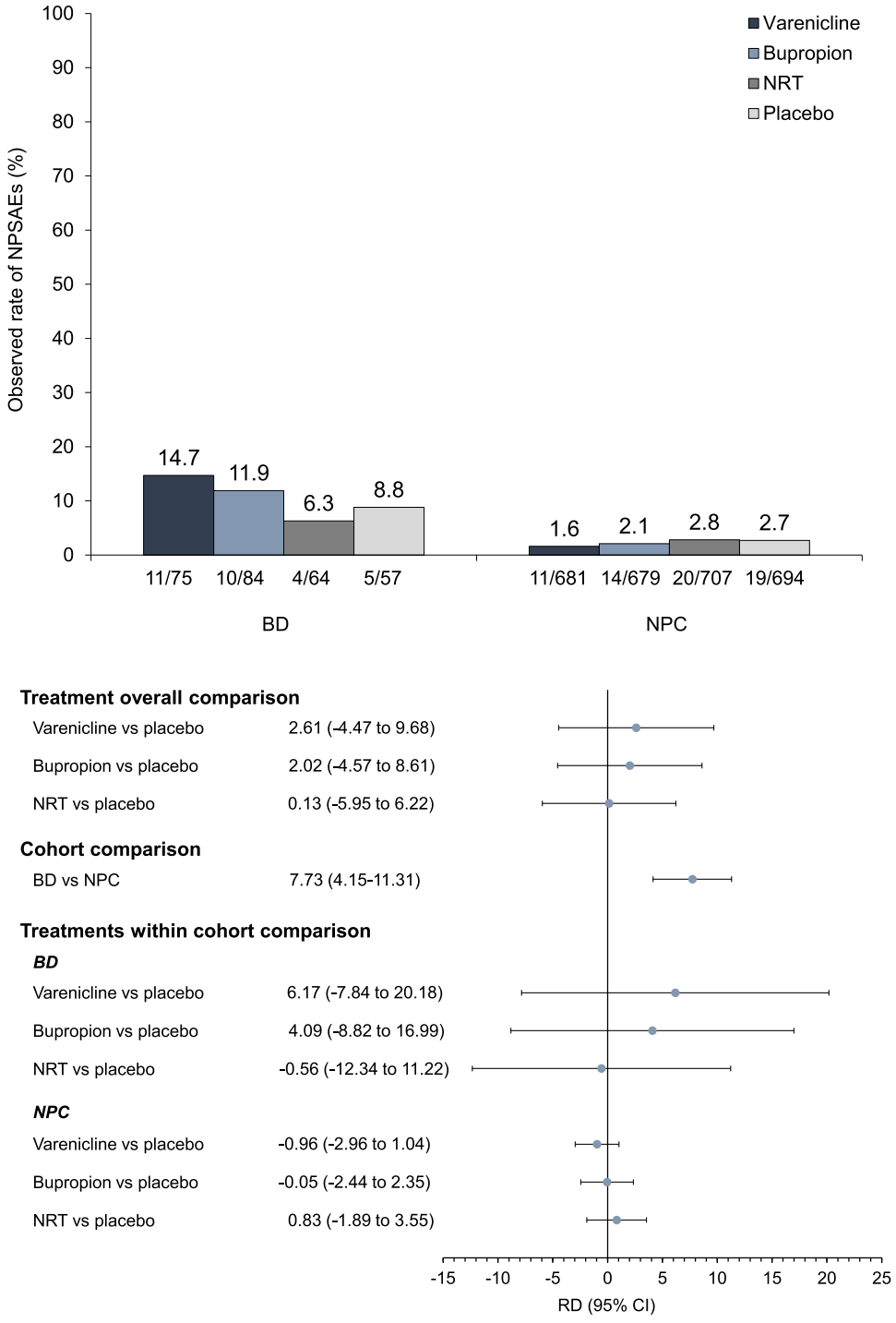

Fig. 1. Incidence of NPSAEs and risk differences in the bipolar disorders subcohort versus nonpsychiatric cohort.
BD, bipolar disorders; CI, confidence interval; NPC, nonpsychiatric cohort; NPSAE, neuropsychiatric adverse event; NRT, nicotine replacement therapy (transdermal nicotine patch); RD, risk difference.
Period for ascertainment of NPSAEs is during 12 weeks of treatment and ≤30 days after last dose.

subcohort (Fig. 3). For combined treatments, the NPC had significantly higher abstinence rates than the BD subcohort (22.8% versus 13.3%; OR, 0.65; 95% CI: 0.43 to 0.97; $P = 0.03$) (Fig. 3).

Weeks 9–24 CARs for the BD subcohort were: varenicline, 12.0%; bupropion, 8.1%; NRT, 4.6%; placebo, 6.8% (eFigure 2 in the **Supplement**). ORs for active treatment versus placebo in the BD subcohort were: varenicline, 1.79 (95% CI: 0.35 to 9.26); bupropion, 1.38 (95% CI: 0.25 to 7.52); and NRT, 0.63 (95% CI: 0.08 to 4.91). Similar to the Weeks 9–12 CARs results, we found main effects of treatment group and cohort with no significant treatment-by-cohort interaction for the secondary smoking abstinence outcome of Weeks 9–24 CAR. Across cohorts, varenicline was superior to placebo (OR, 2.44; 95% CI: 1.04 to 5.70; $P = 0.007$) but, unlike CA Weeks 9–12, there were no significant differences between varenicline and the other active treatments in CA Weeks 9–24. Similar to the Weeks 9–12 results, the NPC had higher quit rates across treatment groups than the BD subcohort (15.6% versus 8.1%; OR, 0.61; 95% CI: 0.37 to 1.00; $P = 0.05$) (eFigure 2 in the **Supplement**).

Table 2
Incidence of neuropsychiatric moderate and severe adverse events (primary endpoint) among treated participants.

	Bipolar disorders subcohort (N = 280)					Nonpsychiatric cohort (N = 2761)				
	All (n = 280)	Varenicline (n = 75)	Bupropion (n = 84)	NRT (n = 64)	Placebo (n = 57)	All (n = 2761)	Varenicline (n = 681)	Bupropion (n = 679)	NRT (n = 707)	Placebo (n = 694)
Observed incidence of the primary composite neuropsychiatric endpoint, n (%)	**30 (10.7)**	11 (14.7)	10 (11.9)	4 (6.3)	5 (8.8)	**64 (2.3)**	11 (1.6)	14 (2.1)	20 (2.8)	19 (2.7)
Estimated primary composite neuropsychiatric endpoint,% (95% CI)	**9.64 (5.90–13.37)**	13.4 (5.18–21.58)	11.3 (4.28–18.31)	6.7 (0.84–12.46)	7.2 (0.08–14.35)	**1.90 (0.38–3.42)**	1.0 (–0.85 to 2.82)	1.9 (–0.13 to 3.93)	2.8 (0.87–4.68)	1.9 (0.06–3.83)
Observed components of primary composite neuropsychiatric endpoint ≥ 1% in any treatment group, n (%)										
Feeling abnormal	**1 (0.4)**	0 (0.0)	1 (1.2)	0 (0.0)	0 (0.0)	**0 (0.0)**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Agitation	**10 (3.6)**	3 (4.0)	3 (3.6)	1 (1.6)	3 (5.3)	**41 (1.5)**	9 (1.3)	8 (1.2)	16 (2.3)	8 (1.2)
Aggression	**1 (0.4)**	0 (0.0)	1 (1.2)	0 (0.0)	0 (0.0)	**9 (0.3)**	2 (0.3)	3 (0.4)	1 (0.1)	3 (0.4)
Hallucinations	**1 (0.4)**	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	**0 (0.0)**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Mania	**13 (4.6)**	5 (6.7)	5 (6.0)	0 (0.0)	3 (5.3)	**1 (< 0.1)**	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Panic	**3 (1.1)**	0 (0.0)	0 (0.0)	3 (4.7)	0 (0.0)	**5 (0.2)**	0 (0.0)	1 (0.1)	1 (0.1)	3 (0.4)
Suicidal ideation	**1 (0.4)**	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	**5 (0.2)**	0 (0.0)	0 (0.0)	2 (0.3)	3 (0.4)
Observed events in the primary composite neuropsychiatric endpoint of severe intensity only, n (%)	**6 (2.1)**	3 (4.0)	2 (2.4)	0 (0.0)	1 (1.8)	**11 (0.4)**	1 (0.1)	3 (0.4)	3 (0.4)	4 (0.6)
Observed components of primary composite neuropsychiatric endpoint of severe intensity only and ≥ 1% in any treatment group, n (%)										
Depression	**1 (0.4)**	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	**1 (< 0.1)**	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Feeling abnormal	**1 (0.4)**	0 (0.0)	1 (1.2)	0 (0.0)	0 (0.0)	**0 (0.0)**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Agitation	**1 (0.4)**	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.8)	**2 (0.1)**	0 (0.0)	0 (0.0)	2 (0.3)	0 (0.0)
Mania	**3 (1.1)**	2 (2.7)	1 (1.2)	0 (0.0)	0 (0.0)	**0 (0.0)**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Events in the primary endpoint, n (%)										
Serious adverse events	**7 (2.5)**	3 (4.0)	4 (4.8)	0 (0.0)	0 (0.0)	**5 (0.2)**	0 (0.0)	1 (0.1)	2 (0.3)	2 (0.3)
Resulting in permanent treatment discontinuations	**16 (5.7)**	5 (6.7)	7 (8.3)	1 (1.6)	3 (5.3)	**13 (0.5)**	1 (0.1)	3 (0.4)	6 (0.8)	3 (0.4)
Combined serious adverse events, severe adverse events, and leading to treatment discontinuations or interventions (≥ 1 of)	**22 (7.9)**	9 (12.0)	7 (8.3)	2 (3.1)	4 (7.0)	**23 (0.8)**	2 (0.3)	6 (0.9)	7 (1.0)	8 (1.2)
C-SSRS-ascertained suicidal ideation and/or behavior, n (%)[b]	**11**[a] **(3.9)**	6[a] (8.1)	2 (2.4)	1 (1.6)	2 (3.5)	**20 (0.7)**	9 (1.3)	3 (0.4)	4 (0.6)	4 (0.6)
Ideation	**11**[a] **(3.9)**	6[a] (8.1)	2 (2.4)	1 (1.6)	2 (3.5)	**20 (0.7)**	9 (1.3)	3 (0.4)	4 (0.6)	4 (0.6)
Behavior	**1**[a] **(0.4)**	1[a] (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	**2 (< 0.1)**	0 (0)	1 (0.1)	1 (0.1)	0 (0)

CI, confidence interval; C-SSRS, Columbia Suicide Severity Rating Scale; NRT, nicotine replacement therapy (transdermal nicotine patch).

[a] C-SSRS was not available for one subject in the varenicline treatment group.

[b] Not all C-SSRS-captured reports of suicidal ideation were considered adverse events or met criteria as moderate to severe neuropsychiatric adverse events.

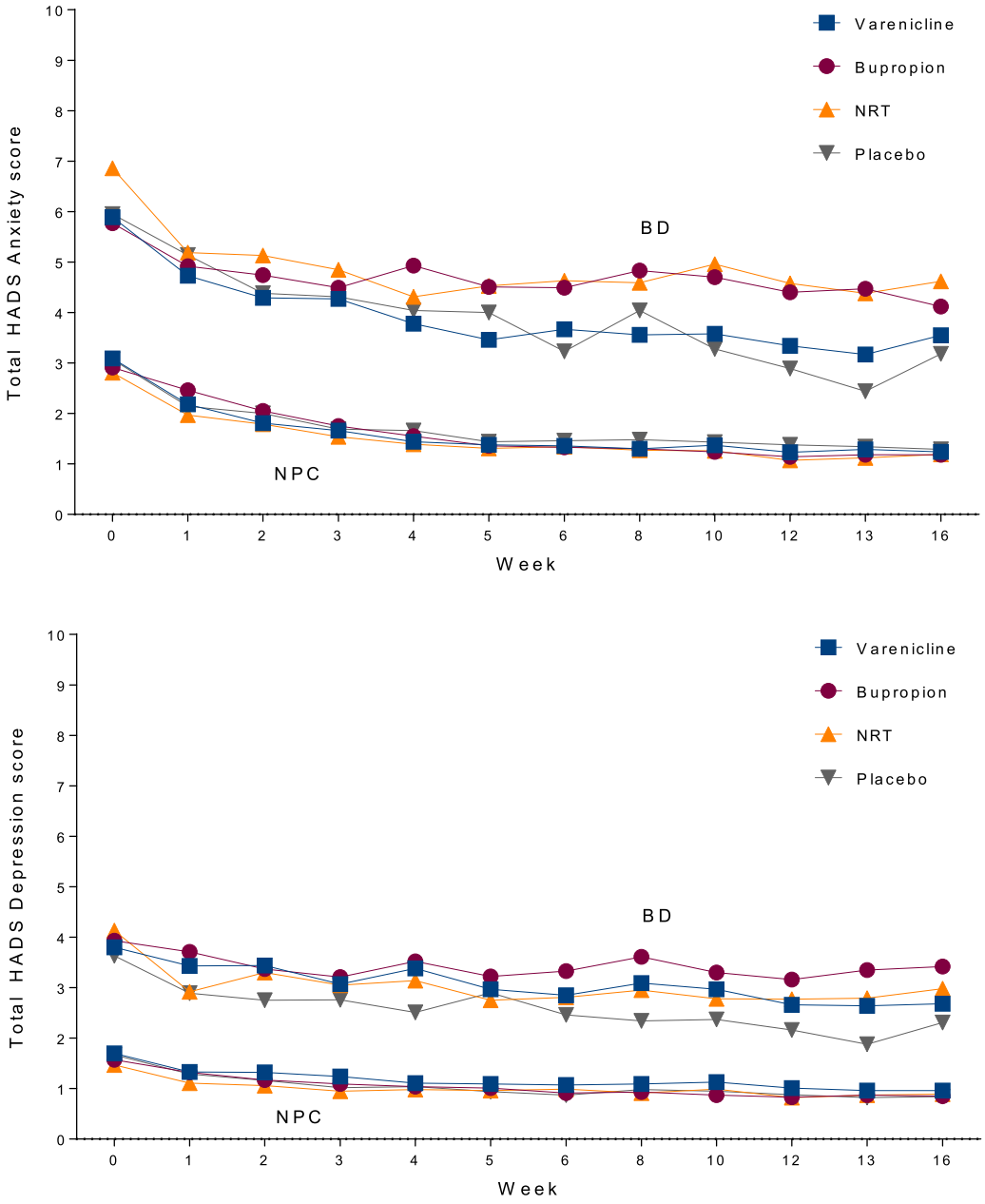

Fig. 2. Hospital Anxiety and Depression Scale scores during treatment and 30-day follow-up.
BD, bipolar disorders; HADS, Hospital Anxiety and Depression Scale; NPC, nonpsychiatric cohort; NRT, nicotine replacement therapy (transdermal nicotine patch).

On the basis of both CA (Fig. 3) and weekly PPA (Fig. 4) outcome data, it is evident that the lack of a statistically significant effect of bupropion and NRT on cessation is driven in large part by the BD subcohort, for which there was evidence of varenicline efficacy but little evidence of bupropion or NRT efficacy. Figs. 3 and 4 illustrate: (1) in the NPC, a pattern of results in which bupropion and NRT clearly fall between varenicline (highest) and placebo (lowest) in terms of efficacy, and (2) a different pattern of results in the BD subcohort, where bupropion and NRT are closer to placebo quit rates and only varenicline (highest) seems to have an effect on abstinence, as evidenced by the 7-day PPA at Week 12 secondary endpoint (OR, 2.93; 95% CI: 1.15 to 7.51). Fig. 4 also illustrates that, while these differences are most apparent at the end of the treatment period, the same patterns are observable throughout the follow-up period.

3.4. Post hoc analysis: relationship between smoking abstinence and moderate to severe NPSAE occurrence

To evaluate the extent to which the numerically higher incidence of moderate to severe NPSAEs among BD smokers assigned to varenicline might be a function of higher rates of smoking abstinence or reduction in the varenicline group (i.e., abstinence-induced NPSAEs), we generated brick plots that show the onset of NPSAE occurence as it relates to weekly changes in smoking status (where abstainer = no smoking during that week; partial abstainer = abstinent for 3–6 days; and smoker = abstinent for 0–2 days) (eFigure 3 in the **Supplement**). We defined a potential abstinence-induced NPSAE as one in which the NPSAE occurred either during the same week or in the week following a significant decrease in smoking (i.e., a transition from a smoker to a partial abstainer or full abstainer, or a transition from a partial abstainer to a full abstainer). Within the BD subcohort, there was no indication that NPSAE variability across treatment groups was driven by

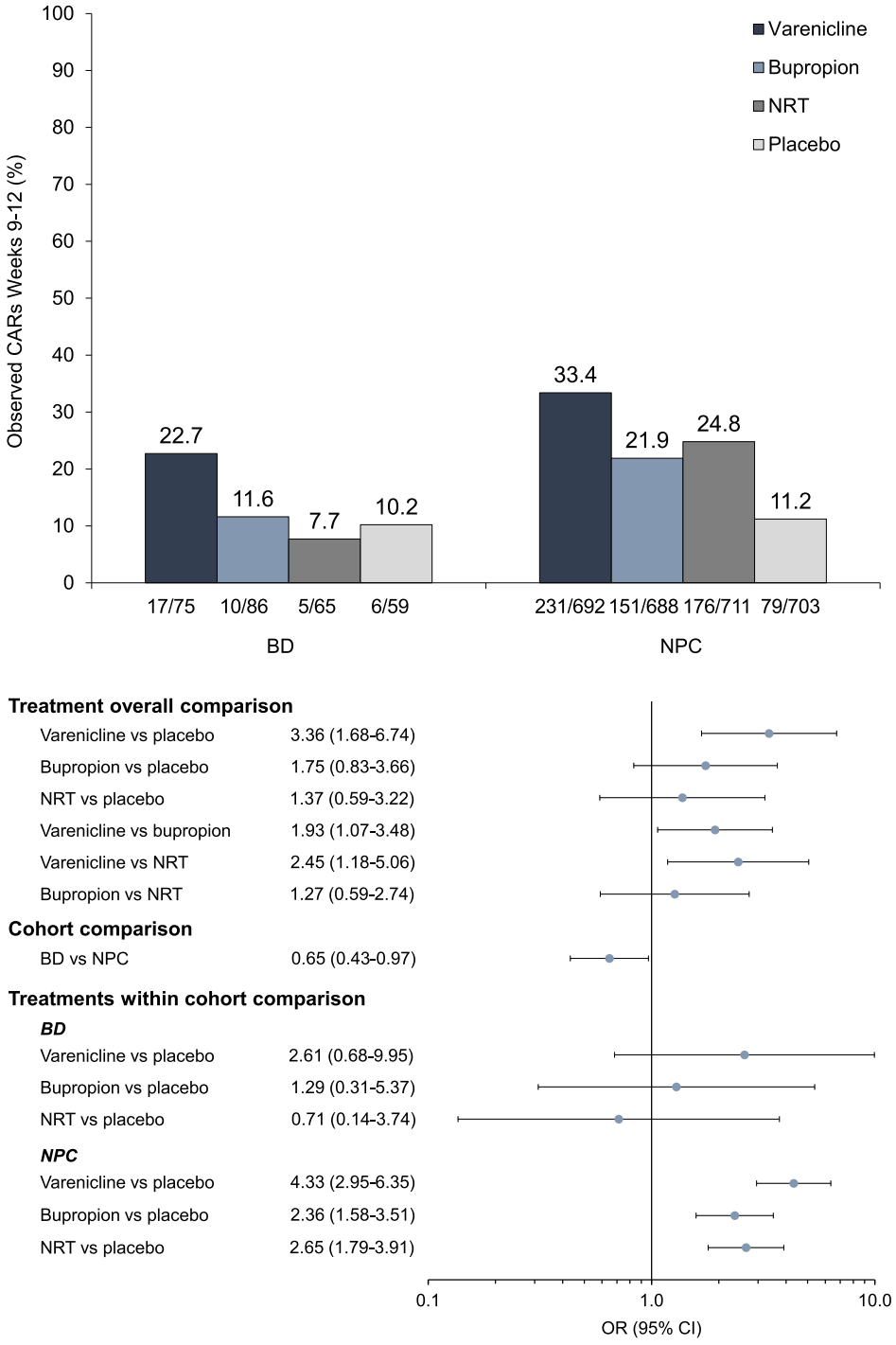

Fig. 3. Observed continuous abstinence rates for Weeks 9–12.
BD, bipolar disorders; CAR, continuous abstinence rate; CI, confidence interval; NPC, nonpsychiatric cohort; NRT, nicotine replacement therapy (transdermal nicotine patch); OR, odds ratio.

smoking abstinence. The number of potential abstinence-induced NPSAEs by treatment group in the BD subcohort was: 1/11 for varenicline, 2/10 for bupropion, 1/4 for NRT, and 1/5 for placebo. Furthermore, the proportions of potentially abstinence-induced NPSAEs were, in most cases, descriptively higher in the NPC: 6/11 for varenicline, 5/14 for bupropion, 7/20 for NRT, and 4/19 for placebo.

4. Discussion

Results from this study suggest that, for smokers with BD who used an FDA-approved cessation medication, change in the risk of experiencing a clinically significant NPSAE during a cessation attempt ranged from a one percentage point decrease to a six percentage point increase relative to placebo. Efficacy of varenicline was supported by the estimated effect size for the BD subcohort (OR, 2.6) as well as the statistically significant difference from placebo on the secondary endpoint of 7-day PPA at end of treatment. Bupropion and NRT effect-size estimates in the NPC of this country-matched sample (i.e., ORs > 2 for CA Weeks 9–12) and, as reported in the main outcome paper (Anthenelli et al., 2016), for the broader psychiatric cohort overall (OR, 1.9 for

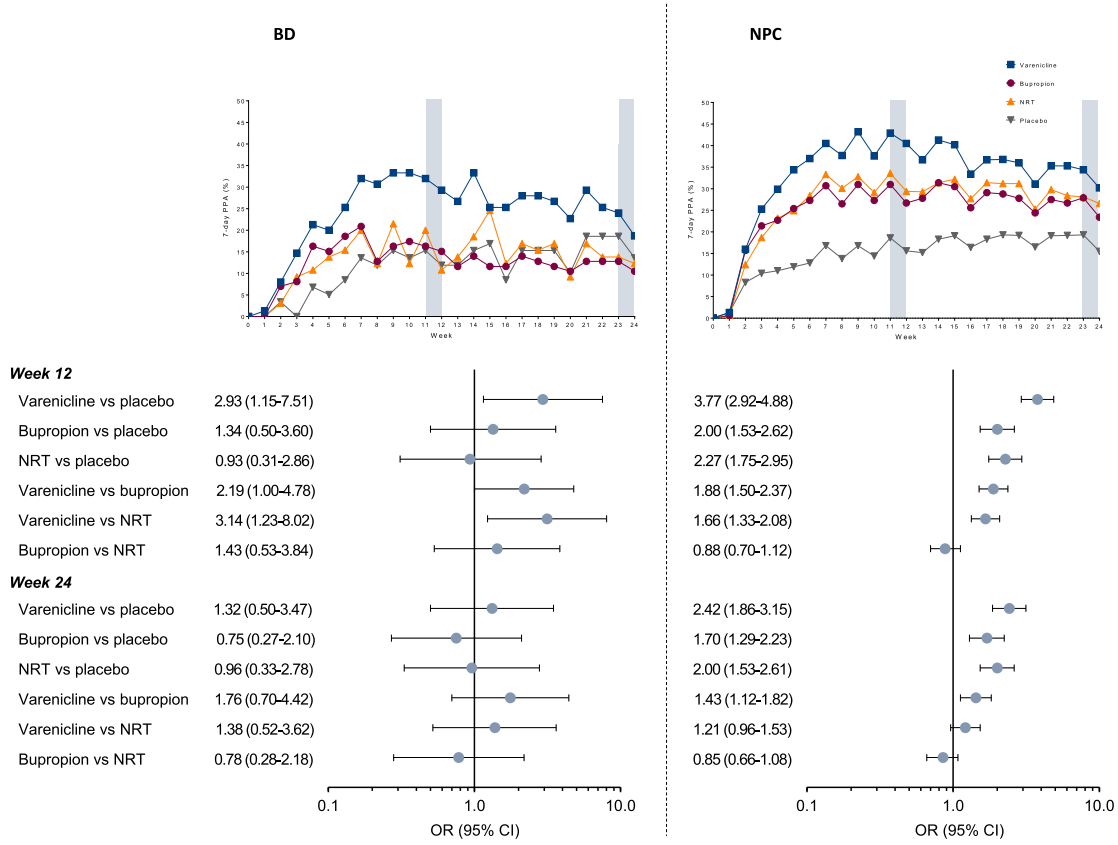

Fig. 4. Observed 7-day point prevalence abstinence during treatment and follow-up.
BD, bipolar disorders; CI, confidence interval; NPC, nonpsychiatric cohort; NRT, nicotine replacement therapy (transdermal nicotine patch); OR, odds ratio; PPA, point prevalence abstinence.

bupropion; OR, 2.0 for NRT) were consistent with previous research showing that these two medications have a similar effect of doubling quit rates relative to placebo (Fiore et al., 2008). In contrast, there was little evidence of efficacy in the BD subcohort, where the observed CA Weeks 9–12 for NRT was descriptively *lower* versus placebo (7.7% versus 10.2%; OR, 0.7), with only a slightly better quit rate for bupropion versus placebo (11.6% versus 10.2%; OR, 1.3).

To date, only one other randomized controlled trial of smokers with BD enrolled enough participants ($n = 60$) to compare a smoking cessation treatment with placebo in this population (Chengappa et al., 2014). This trial also indicated that varenicline is effective for smokers with BD and that, relative to placebo, there is no evidence that varenicline substantially increases the risk of moderate to severe NPSAEs. Varenicline may increase the risk of less severe events such as sleep disturbance (e.g., abnormal dreams, insomnia). We also observed descriptively higher rates of sleep disturbance with varenicline versus placebo in the BD subcohort (26.7% versus 10.5%) as well as in the NPC (22.5% versus 14.3%). However, given the well-documented associations between smoking abstinence or reduction and sleep disturbance (Patterson et al., 2017), it is difficult to disentangle effects of cessation medications from effects of decreased smoking. In the case of the primary safety outcome of moderate to severe NPSAE occurrence, our post hoc analysis suggested that descriptively higher NPSAE rates among smokers with BD who received varenicline were not driven by smoking abstinence or reduction. It is also worth noting that the timing of these events showed no clear association with the initiation of the medication (eFigure 3 in the **Supplement**).

Although this is the first prospective study to demonstrate that smokers with BD had higher NPSAE incidence and lower quit rates than those without lifetime psychiatric illness, these findings are not surprising. The finding of a 40–50% lower quit rate for smokers with BD relative to the NPC (i.e., 22.8 versus 13.3% for Week 9–12 CAR; 15.6% versus 8.1% for Week 9–24 CAR) is consistent with findings from previous epidemiologic studies showing that quit rates (i.e., the ratio of former to ever smokers) are 60% lower among people with bipolar disorder relative to people with no mental health conditions (Lasser et al., 2000). Of importance to treatment providers and to smokers with BD, the estimated differences in risk of clinically significant NPSAE occurrence between active treatments and placebo within the BD subcohort were relatively small: 6% or less across treatments. Further, this analysis provides clinically useful information on relative abstinence rates with varenicline, bupropion, and NRT in the largest cohort of smokers with BD studied to date. Our findings support the efficacy of varenicline and raise questions about the efficacy of NRT monotherapy and bupropion for this group.

Several limitations of the study findings should be noted. Combination NRT, which is more effective than NRT monotherapy (Fiore et al., 2008), was not included as a comparison treatment, leaving open the question of comparative safety and efficacy of this treatment option for smokers with BD. Additionally, the findings may not generalize to smokers with BD whose symptoms are unstable, who are not taking psychotropic medications, or who have current substance use disorders. Similarly, the BD subcohort was predominantly (81%) composed of individuals who met diagnostic criteria for BD I, limiting generalizability to smokers with BD II. EAGLES was not powered to test treatment safety and efficacy in the BD subcohort; therefore, definitive conclusions cannot be drawn about lack of statistically significant effects, and these results should be considered exploratory. With regard to biochemical verification of abstinence, EAGLES used a CO cut-off level that does not preclude very light smoking. Although this was the standard recommendation at the time the trial was designed (Benowitz et al., 2002), lower CO cut-offs to establish smoking

abstinence have subsequently been recommended (Marrone et al., 2011; Perkins et al., 2013). While not a study limitation per se, the design of the EAGLES trial precludes an examination of some mechanisms that may underlie the differences in cessation outcomes between smokers with BD and those with no psychiatric history (e.g., substance use disorder history, which was present in 40% of the BD subcohort but was exclusionary for the NPC). Consequently, it is not possible to determine, for example, whether lower quit rates in the BD subcohort are attributable to the direct effects of having BD or to indirect effects of having BD (e.g., BD increases risk of substance abuse disorders, which increase risk of cessation failure). We also note that inferences about the quit rates for the NPC in this analysis ($n = 2794$) should be tempered by the fact that this is a subgroup of the NPC in the larger EAGLES trial ($N = 4028$) that excludes a significant portion of the non-US participants. Because quit rates were lower for US smokers in EAGLES (West et al., 2018), this led to a decrease in the quit rates for the NPC group in this subgroup analysis since a larger proportion of the sample was from the US (68% in this analysis versus 47% in the larger trial).

EAGLES is the largest-ever evaluation of cessation pharmacotherapies and one of very few pharmacotherapy trials to include smokers with serious mental illness, with rigorous methods of confirming psychiatric diagnoses via comprehensive diagnostic interviews. Consequently, EAGLES provided a one-of-a-kind opportunity to evaluate safety and efficacy outcomes for the subgroup of smokers with BD using a sample size over four times greater than the largest trial previously published on this population (Chengappa et al., 2014). Additionally, this study is the first to report on the following for smokers with BD: a placebo-controlled evaluation of the efficacy of NRT monotherapy; safety and efficacy data for the three major FDA-approved cessation therapies when delivered in conjunction with behavioral counseling; and a comparison of the safety and efficacy of these treatments in smokers with BD versus those without a psychiatric disorder.

In conclusion, the results suggest that varenicline, in combination with behavioral support, may be the best option of the three active treatments in this study given its greater efficacy effect size and similar risk of moderate to severe NPSAEs. Observed effect sizes for NRT monotherapy and bupropion versus placebo suggest that they may not be effective aids to cessation in smokers with BD. Results also suggested that most (89%) smokers with BD did not experience a clinically significant NPSAE during a quit attempt. Relative to smokers without mental health conditions, however, they are at greater risk for moderate to severe NPSAEs during a quit attempt and are less likely to quit, regardless of which treatment they receive and even after controlling for demographics, smoking, and prior cessation medication usage. The mechanisms through which smokers with BD experience worse cessation outcomes and greater likelihood of NPSAEs requires additional study. Candidate mechanisms include differences highlighted in the present study results (e.g., for the BD subcohort, more severe nicotine dependence on the FTCD, which was predictive of poorer cessation outcomes in the broader study (West et al., 2018); higher baseline levels of anxiety, depression, aggression; and greater likelihood of past suicidal ideation and behavior), as well as the potential influence of some psychotropic medications on nicotine metabolism among smokers with BD (Williams et al., 2012), which may impact pharmacotherapy response (Lerman et al., 2015; Schnoll et al., 2009).

Improved understanding of mechanisms underlying greater cessation difficulty and NPSAE occurrence among smokers with BD can help to inform new treatment approaches to address disparities in treatment outcomes. Although this remains a nascent area of research, a novel behavioral treatment (Acceptance and Commitment Therapy) that targets barriers to quitting among smokers with BD has been piloted, with promising results (Heffner et al., 2015). Longer courses of pharmacotherapy and abstinence-contingent monetary incentives (Brunette et al., 2018; Evins et al., 2014) may also improve cessation outcomes for smokers with BD, as well as those with other forms of serious mental illness.

Authors' contributions

All authors, JLH, AEE, CR, DL, CRA, TMR, LSA, AK, RW, and RMA, were involved in the analyses and/or interpretation of data; DL performed the statistical analyses; JLH drafted the initial manuscript; all authors have critically revised the manuscript for content and have approved the final version.

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CRediT authorship contribution statement

Jaimee L. Heffner: Conceptualization, Writing - review & editing, Writing - original draft. **A. Eden Evins:** Conceptualization, Writing - review & editing. **Cristina Russ:** Conceptualization, Writing - review & editing. **David Lawrence:** Conceptualization, Writing - review & editing, Formal analysis. **Catherine R. Ayers:** Conceptualization, Writing - review & editing. **Thomas McRae:** Conceptualization, Writing - review & editing. **Lisa St. Aubin:** Conceptualization, Writing - review & editing. **Alok Krishen:** . **Robert West:** Conceptualization, Writing - review & editing. **Robert M. Anthenelli:** Conceptualization, Writing - review & editing.

Declaration of Competing Interest

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2019.06.008.

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