Efficacy and Safety of Pharmacotherapeutic Smoking Cessation Aids in Those With Schizophrenia Spectrum Disorders: A Subgroup Analysis of EAGLES

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Abstract

Objective: Evaluate efficacy and safety of varenicline, bupropion, and nicotine replacement therapy (NRT) for smoking cessation in smokers with schizophrenia spectrum disorders in *post-hoc* analyses of EAGLES data.

Methods: Smokers with a schizophrenia spectrum disorder (n=390) and without a psychiatric illness (controls) (n=4,028) were randomly assigned to varenicline, bupropion, NRT, or placebo for 12 weeks. Outcomes included abstinence rates during treatment and follow-up, number needed to treat (NNT) for abstinence, incidence of neuropsychiatric adverse events, and temporal relationship between neuropsychiatric adverse events and abstinence status.

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Results: Smokers with schizophrenia smoked more, had greater dependence, and fewer prior trials of cessation pharmacotherapy. At each timepoint, on varenicline, smokers with schizophrenia had significantly greater odds of abstinence than placebo and comparable NNT with controls. Bupropion and NRT increased odds of abstinence, though confidence intervals included one for some comparisons and produced greater NNT in smokers with schizophrenia than controls. No treatment was associated with significantly more neuropsychiatric adverse events than placebo in either cohort. The estimated neuropsychiatric adverse event rate was 5% (95% CI=3.0–7.7) in smokers with schizophrenia and 1% (95% CI=.6–2.1) in controls. Over one-third of neuropsychiatric adverse events occurred during partial or full abstinence, suggesting a multifactorial nature of neuropsychiatric adverse events.

Conclusions: In smokers with schizophrenia, varenicline was associated with significantly higher abstinence rates than NRT, bupropion, and placebo, and had NNT comparable with smokers without psychiatric disorders. A significant proportion of neuropsychiatric adverse events occurred during early abstinence. No treatment significantly increased neuropsychiatric adverse event prevalence.

BACKGROUND

People with schizophrenia spectrum disorders are more likely to smoke tobacco, smoke heavily (1), and have severe dependence than those without psychiatric illness (2–4). Smoking rates are not decreasing for those with schizophrenia as they are in the general population (5), and smoking-related disease contributes disproportionately to a comparative 29-year mortality gap in adults (6–9). Though quitting smoking by middle age reduces the risk of death associated with continued smoking by 90% (10), smokers with schizophrenia are less likely than those in the general population to be offered effective pharmacotherapeutic smoking cessation aids, particularly varenicline (1, 11, 12). Consistent reports of abstinence rates <5% in smokers with schizophrenia with behavioral smoking cessation treatment alone (13–19) suggest that this group particularly needs pharmacotherapeutic cessation aids to quit smoking.

Despite evidence for safety and efficacy of first-line pharmacotherapeutic cessation aids in this population (19, 20), clinicians report negative attitudes toward providing smoking cessation treatment for smokers with schizophrenia (21), with pharmacotherapy— particularly non-nicotine pharmacotherapy—being particularly underutilized (1, 11, 12, 22, 23). Additionally, Medicaid coverage of the most effective cessation treatments remains limited in many US states despite legislation barring state Medicaid programs from excluding US Food and Drug Administration (FDA)-approved cessation medications from coverage (24). High co-pays and prior authorization requirements remain common barriers to obtaining smoking cessation medication through Medicaid and Medicare plans that insure most people with schizophrenia spectrum disorders (25). Additionally, limits on access to effective smoking cessation treatment, through low rates of prescribing and financial barriers, place people with schizophrenia at increased risk for smoking-related disease and death.

The neuropsychiatric safety and efficacy trial of varenicline, bupropion, and nicotine replacement therapy (NRT) in smokers with and without psychiatric disorders (EAGLES) estimated the incidence of moderate to severe neuropsychiatric adverse events (NPSAEs) during a 12-week treatment period and 12-week follow-up, and assessed tobacco abstinence rates (26). Neuropsychiatric adverse event incidence and continuous abstinence rates have been reported for the schizophrenia spectrum disorders subcohort relative to the mood and anxiety disorders subcohorts (27). To address safety concerns that may drive the particular underuse of effective smoking cessation medications in smokers with schizophrenia, we undertook a *post-hoc* analysis of weekly patterns of neuropsychiatric adverse events and abstinence rates in the EAGLES schizophrenia spectrum disorders subcohort versus smokers without psychiatric disorders, including analysis of timing of neuropsychiatric adverse events relative to start of study medication and change in weekly 7-day point prevalence abstinence (PPA) status, and analysis of end-of-treatment abstinence rates by baseline psychiatric symptom severity rating.

METHODS

EAGLES was a multinational, multicenter, randomized, double-blind, placebo- and active (NRT)-controlled trial, conducted from November 30, 2011 to January 13, 2015. The primary report provides details of the design and primary outcomes (26). Study procedures and consent forms were approved by the institutional review boards at participating institutions. All participants signed informed consent.

Eligible participants were motivated-to-quit adults, aged 18–75 years, who smoked 10 cigarettes per day, with exhaled carbon monoxide (CO) >10 parts per million (ppm) at screening. Eligible smokers with schizophrenia spectrum disorders met *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (DSM-IV-TR) (28) diagnostic criteria for current or lifetime psychotic disorders including schizophrenia and schizoaffective disorders and were not excluded for other prespecified psychiatric comorbidities that excluded alcohol and other substance use disorders within the previous 12 months. Smokers with schizophrenia spectrum disorders made up approximately 10% of the psychiatric cohort (n=390) in EAGLES. Enrolment criteria required a score of <5 on the 7-point Clinical Global Impression–Severity (CGI-S)(29), indicating moderate severity of symptoms or less. The control cohort without psychiatric disorders (n=4,028) had no Axis I diagnosis.

Randomization, masking, and study treatment

Randomization to varenicline 1 mg twice-daily, bupropion sustained-release 150 mg twice-daily, NRT transdermal patch 21 mg per day with taper, or placebo was done in a 1:1:1:1 ratio with block size of eight for each diagnostic subcohort by region in a double-blind, triple-dummy, parallel-group design.

Participants set a target quit-date 1 week post-randomization, coinciding with the end of varenicline and bupropion up-titration and initiation of NRT. Study visits were weekly for 6 weeks, biweekly for 6 weeks, then at weeks 13, 16, 20, and 24. Ten-minute individual

smoking cessation counseling was provided at each visit (30). Telephone contacts to determine smoking status were conducted weekly between visits.

Assessments

Psychiatric diagnosis was assessed at screening with the Structured Clinical Interviews for DSM-IV-TR Axis I and II Disorders (SCID-I and SCID-II) (28, 31). Severity of cigarette dependence was assessed with the Fagerström Test for Cigarette Dependence (FTCD) (32).

Abstinence was assessed weekly, defined as self-report of tobacco abstinence since the previous study assessment. Expired CO   10 ppm was used to validate self-reported abstinence. CO was collected at study weeks 1–6, 8, 10, 12, 16, and 24. Participants who discontinued the study or were lost to follow-up or had missing CO data at weeks 12 or 24 were considered non-abstinent.

A neuropsychiatric adverse event was an adverse event in one of 16 neuropsychiatric symptom categories volunteered, observed, or solicited during treatment or 30-day follow-up that was new or increased in severity from baseline, irrespective of whether the adverse event was considered causally related to study medication, that met *a priori* severity criteria. Neuropsychiatric adverse events expected to be more common (anxiety, depression, feeling abnormal, or hostility) that were rated as severe, and those in agitation, aggression, delusions, hallucinations, homicidal ideation, mania, panic, paranoia, psychosis, suicidal ideation, behavior, or suicide categories rated as moderate or severe met criteria as a neuropsychiatric adverse event.

Neuropsychiatric adverse events were assessed at each study visit with open-ended questions, direct observation, and the semi-structured Neuropsychiatric Adverse Event Interview (26, 33). Positive responses on the Neuropsychiatric Adverse Event Interview were evaluated for frequency, duration, and severity to determine if they qualified. Investigators evaluated whether positive responses on the Columbia Suicide Severity Rating Scale (C-SSRS) or proxy reports from family members or others were NPSAEs. Psychiatric symptoms were assessed at each study visit with the Hospital Anxiety and Depression Scale (34) and C-SSRS (35). Tobacco and nicotine use were assessed with a structured questionnaire and expired CO measurement.

Analysis

Generalized linear models (GLMs) were conducted to test the effect of treatment (varenicline, bupropion, NRT, placebo), and cohort (schizophrenia spectrum disorders, no psychiatric disorders) on 7-day PPA and continuous abstinence rates during the treatment and follow-up periods. Observed rates of NPSAEs were reported and GLMs were conducted to test effects of treatment, cohort, and their interaction on the NPSAE primary endpoint for 16 weeks following treatment initiation (12 weeks treatment and 4 weeks follow-up). All models included region and age, race, body mass index (BMI), smoking characteristics, and past cessation medication use if associated with outcome (36). For each reported NPSAE the week of the event was plotted together with change in weekly 7-day PPA status: smoker, partial abstainer, abstainer, by treatment assignment and cohort.

RESULTS

Participants

The efficacy cohort consisted of all 390 and 4,028 participants enrolled in the schizophrenia and control cohorts. The safety cohort consisted of 386 (99%) and 3,984 (99%) smokers in the schizophrenia and control cohorts who received 1 dose of study medication. The 12-week treatment and 12-week follow-up phases, respectively, were completed by 350 (90%) and 336 (86%) smokers with schizophrenia and 3,404 (85%) and 3,124 (78%) smokers without psychiatric disorders (CONSORT diagram available online).

In the schizophrenia spectrum disorders subcohort, 303 (78%) met DSM-IV-TR criteria for schizophrenia, and 87 (22%) for schizoaffective disorder, while 142 (36%) met SCID criteria for comorbid Axis I disorder, including 105 (27%) with a prior alcohol or substance abuse disorder. Those in the schizophrenia subcohort were more likely to report suicidal ideation or behavior in their lifetime (32% vs. 5% in those without psychiatric disorders), to report greater symptoms of anxiety, depression, and aggression at baseline, and to be treated with psychotropic medications (Table 1).

Smokers with schizophrenia smoked more cigarettes per day (23.2 vs. 20.7) and had greater severity of cigarette dependence (FTCD total score: 6.9 vs. 5.5) than controls. Smokers with schizophrenia were not significantly less likely to have made a smoking cessation attempt (72% in the schizophrenia subcohort reported a mean 2.4 prior serious quit attempts and 82% of controls reported a mean of 3.2 quit attempts). However, they were significantly less likely than controls to report prior trials of smoking cessation treatment: varenicline (8% vs. 14%), bupropion (4% vs. 9%), and NRT (15% vs. 25%) (Table 1).

Tobacco-smoking abstinence

Seven-day PPA rates at end-of-treatment and follow-up—Weekly observed 7-day PPA rates by treatment are shown in Figure 1a. Odds of 7-day end-of-treatment PPA in smokers with schizophrenia were 6-fold higher with varenicline than placebo and >2-fold higher with varenicline than bupropion or NRT. Odds of 7-day end-of-treatment PPA in smokers with schizophrenia were >2-fold higher with bupropion and NRT than placebo (treatment comparison figure online). NNT in smokers with schizophrenia and controls for 7-day end-of-treatment PPA was: varenicline, five and four; bupropion, 17 and eight; NRT, 12 and eight (Figure 1b).

At week 24, odds of 7-day PPA for active treatments vs. placebo in smokers with schizophrenia ranged from 2.8 for NRT to 5.2 for varenicline. In controls, odds ratios for 7-day PPA for all active treatments were superior to placebo and were superior for varenicline to bupropion and NRT (treatment comparison figure online). The relative efficacy of active treatments was similar across cohorts, and abstinence rates were higher in those without psychiatric disorders (Figure 1a). NNT in smokers with schizophrenia and controls for 7-day PPA at week 24 was: varenicline, seven and seven; bupropion, 13 and 12; NRT, 13 and 11 (Figure 1b).

Figures presenting weekly observed and estimated continuous abstinence rates for weeks 9–12 in a model including treatment, cohort, region, treatment-by-cohort, FTCD, cigarettes/day in the past month, race, age, years smoked, and BMI are available in the online supplement. NNT in smokers with schizophrenia and controls for continuous abstinence, weeks 9–12, was: varenicline, six and five; bupropion, 14 and nine; NRT, 12 and eight.

A table presenting 7-day end-of-treatment PPA rates by baseline CGI-S symptom severity category is online. While abstinence rate was highest among those few with the lowest possible baseline symptom severity, there was no progression to lower abstinence rates with increasing baseline psychiatric symptom burden.

Neuropsychiatric safety during 12 weeks' treatment and 4 weeks' follow-up—
Neuropsychiatric adverse event rates were not significantly higher with any active treatment than placebo overall or in either cohort, and there were no significant treatment by diagnosis interactions (Figure 2); the point estimates are negative in smokers with schizophrenia for varenicline and NRT. There were significant effects for diagnostic cohort, region, and race. Smokers with schizophrenia were more likely than controls to experience a neuropsychiatric adverse event. Observed neuropsychiatric adverse event rates in smokers with schizophrenia were: varenicline, 6%; bupropion, 6%; NRT, 5%; placebo, 6% (table available online).

There were no observed effects of treatment on suicidal ideation or behavior, serious adverse events, or adverse events resulting in permanent discontinuations. In smokers with schizophrenia, NPSAEs in the primary endpoint that were severe, constituted a serious adverse event, or led to treatment discontinuation or an intervention occurred in 2% (varenicline), 1% (bupropion), 2% (NRT), and 2% (placebo). Serious adverse events were observed in <1% in both cohorts (table available online). In smokers with schizophrenia, 22% and in controls, 30% reported an adverse event in the Medical Dictionary for Regulatory Activities psychiatric disorders category of mild, moderate, or severe intensity.

In an exploratory analysis of the temporal relationship between neuropsychiatric adverse event onset with 7-day PPA status, by treatment assignment and cohort, 8/23 (35%) NPSAEs in smokers with schizophrenia and 40/84 (48%) in controls were reported at a study visit when the participant had been partially or fully abstinent in the prior week (figure available online).

DISCUSSION

This analysis provides robust evidence for efficacy of first-line FDA-approved smoking cessation medications—particularly varenicline, in smokers with schizophrenia spectrum disorders and those without psychiatric disorders, where the NNT to obtain end-of-treatment abstinence was 5 and 4—with no clear relationship between baseline psychiatric symptom burden and attainment of abstinence, or between neuropsychiatric adverse events and treatment in either cohort. In both cohorts, odds of 7-day end-of-treatment PPA were higher with varenicline than bupropion, NRT, and placebo, and higher with NRT than placebo. Prior trials have shown efficacy of varenicline (37), bupropion (14, 15), and

bupropion combined with NRT for smoking cessation in smokers with schizophrenia (16, 17). EAGLES is the first trial to report efficacy of NRT vs. placebo for smoking cessation in smokers with schizophrenia.

Considering the greater severity of nicotine dependence and psychiatric symptom burden in smokers with schizophrenia, these participants would be expected to be less likely to quit smoking than smokers without an Axis I psychiatric illness. Interestingly, we report no clear relationship in smokers with schizophrenia between abstinence rates and psychiatric symptom severity, and essentially equivalent NNT for varenicline in smokers with schizophrenia and those without psychiatric disorders (5 vs. 4). While the confidence intervals overlapped, point estimates for odds of abstinence with varenicline were nearly twice as high in smokers with schizophrenia versus controls without psychiatric disorders, likely due to very low abstinence rates for smokers with schizophrenia with placebo, which is consistent with prior reports of 4–5% abstinence rates with behavioral treatment alone (14–16, 19, 37). Such low success rates indicate that it is critical for smokers with schizophrenia to have access to pharmacotherapeutic cessation aids if they are to be successful in their efforts to quit smoking. Varenicline is underutilized in smokers with psychotic illness (11, 12), and in this trial, smokers with schizophrenia reported significantly fewer prior treatment trials with varenicline, bupropion, or NRT—without significantly fewer prior cessation attempts—than smokers without psychiatric disorders.

In light of greater psychiatric symptom burden, higher ratings of anxiety, depression, aggression and nicotine dependence severity, and more prior suicidal ideation/behavior, it is not surprising that those in the schizophrenia subcohort were more likely than controls to experience a neuropsychiatric adverse event during the treatment and follow-up periods. The baseline neuropsychiatric adverse event rate for smokers with schizophrenia outside the context of a smoking cessation attempt is unknown. In smokers with schizophrenia, neuropsychiatric adverse events appear to be multifactorial and sporadic as they did not cluster within any particular symptom domain or shortly after study medication initiation or the quit date, occurred independent of treatment assignment, rarely led to permanent discontinuation of smoking cessation medication, and approximately one-third were reported during study weeks with partial or complete tobacco abstinence. While serious adverse events were observed in <0.5% in the schizophrenia subcohort and 0.2% in the cohort without psychiatric disorders, this is worth weighing against the well-established metric that half of smokers who do not quit will die prematurely from a smoking-related illness.

It is now considered standard of care to offer effective smoking cessation pharmacotherapy to all smokers at every clinical visit (38), even in smokers who report they may not be ready to make a cessation attempt. In considering the risk–benefit ratio of providing smoking cessation treatment to smokers with schizophrenia, several points are worth considering. It is increasingly recognized that smoking cessation itself does not significantly exacerbate the symptoms or course of mental illness (39, 40), and that active treatments that significantly improve abstinence rates in smokers with schizophrenia do not exacerbate psychiatric symptoms (19, 41). In EAGLES, smokers with schizophrenia treated with placebo and behavioral support were as likely as those treated with varenicline, bupropion, or NRT to

experience a moderate to severe neuropsychiatric adverse event, but were far less likely to attain abstinence. The life expectancy for people with schizophrenia is approximately 29 years shorter than those without psychiatric illness, and tobacco smoking is the single largest cause of this disparity in life expectancy (8, 42, 43), while smoking cessation effectively mitigates this risk (10, 44, 45). Because tobacco smoking is associated with increased hepatic clearance of many psychotropic drugs, particularly those metabolized by cytochrome P450 1A2 and 2E1, it is recommended that clinicians monitor patients who reduce or quit smoking for evidence of reduced clearance of psychotropic medications metabolized by these enzymes and consider dose adjustment accordingly (46–48).

Limitations

Though 27% of smokers with schizophrenia had a prior alcohol or substance use disorder, smokers with an active substance use disorder other than nicotine were excluded, so results cannot be expected to generalize to those with active substance use. Likewise, though participants were symptomatic at baseline, enrolment criteria required that psychiatric symptoms be stable, and 95% of smokers with schizophrenia were taking psychotropic medications, thus results cannot be expected to generalize to unstable or untreated smokers with schizophrenia. While increasingly considered standard clinical care, dual NRT (NRT patch plus NRT gum, lozenge, nasal spray, or inhaler) was not tested. Future research is needed to test the effects of dual NRT in smokers with schizophrenia and to compare efficacy and tolerability of dual NRT with varenicline and bupropion. The behavioral component of the intervention was brief; trials of pharmacotherapy plus more intensive behavioral treatment have shown higher abstinence rates in smokers with schizophrenia (49). Further research is needed to determine whether more intensive behavioral treatment improves efficacy of pharmacotherapy for nicotine dependence in smokers with schizophrenia. We report 24 weeks' efficacy data and 16 weeks' safety data, though clinicians and smokers will be interested in longer-term outcomes (49, 50).

CONCLUSION

Tobacco smokers, particularly smokers with schizophrenia, need help to quit. We provide robust evidence for efficacy and tolerability for smoking cessation treatments, particularly varenicline. These data, together with strong evidence that smoking cessation does not exacerbate mental illness (19, 39), strong consistent evidence for low abstinence rates in smokers with schizophrenia with behavioral treatment alone (19, 22), and benefit of smoking cessation on premature mortality (10, 44) should spur lowering of barriers, at the policy and practitioner level, to greater utilization of the most effective pharmacotherapeutic cessation aids for those with smokers with schizophrenia as standard of care.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments:

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Highlights

- Smokers with schizophrenia spectrum disorders smoked more cigarettes per day, had greater severity of cigarette dependence, and had fewer prior trials of smoking cessation pharmacotherapy than smokers without Axis I psychiatric disorders though they had not made significantly fewer quit attempts.

- In smokers with schizophrenia spectrum disorders, smoking cessation pharmacotherapy with varenicline was associated with higher abstinence rates than with NRT or bupropion.

- The number needed to treat with varenicline was comparable in smokers with schizophrenia spectrum disorders and those without a psychiatric disorder.

- None of the active smoking cessation pharmacotherapies significantly increased the prevalence of neuropsychiatric adverse events in either smokers with schizophrenia spectrum disorders or those without a psychiatric disorder.
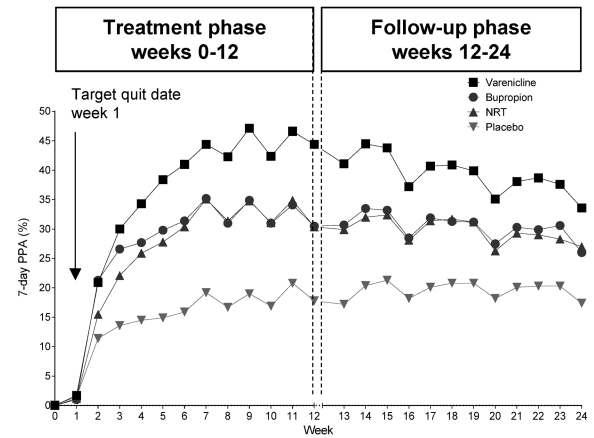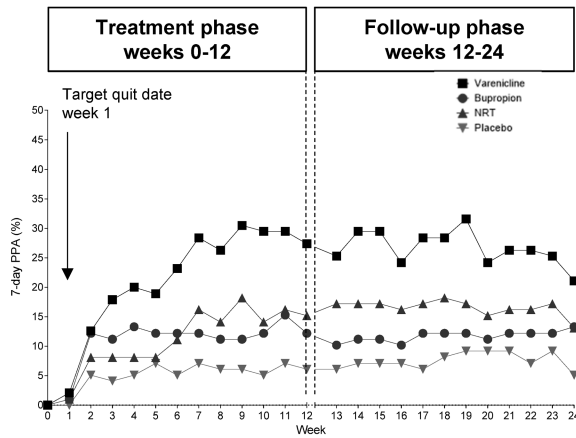
Figure 1. a) Observed 7-day point prevalence abstinence rates at each study visit, and b) number needed to treat for 7-day point prevalence abstinence at end of treatment and end of follow-up

NRT, nicotine replacement therapy (transdermal nicotine patch); PPA, point prevalence abstinence.

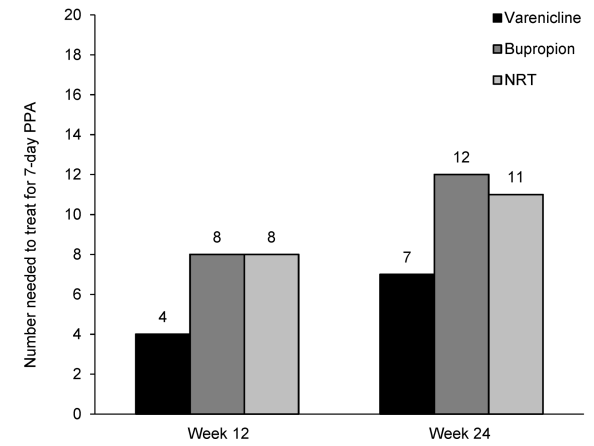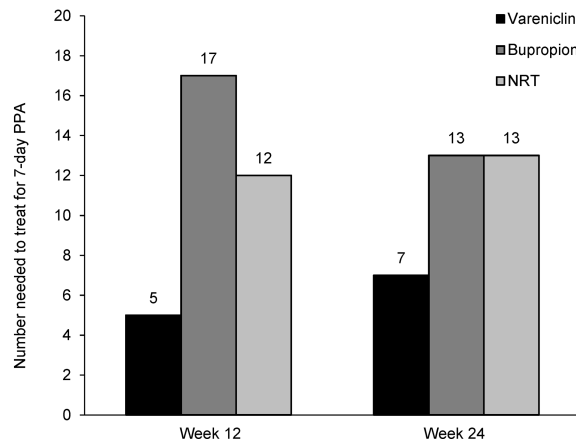| Comparisons	RD (95% CI)
Treatments	
Varenicline vs. placebo	−1.54 (−6.09, 3.01)
Bupropion vs. placebo	0.01 (−4.34, 4.36)
NRT vs. placebo	−1.06 (−5.31, 3.20)
Treatments within cohorts	
Schizophrenia spectrum disorders	
Varenicline vs. placebo	−1.87 (−10.86, 7.11)
Bupropion vs. placebo	0.05 (−8.46, 8.57)
NRT vs. placebo	−2.65 (−11.06, 5.75)
No psychiatric disorders	
Varenicline vs. placebo	−1.21 (−2.72, 0.30)
Bupropion vs. placebo	−0.03 (−1.74, 1.67)
NRT vs. placebo	0.54 (−1.62, 2.70)
Cohorts	
Schizophrenia spectrum disorders vs. no psychiatric disorders	3.96 (1.63, 6.29)
Region	
Non-US vs. US	−1.87 (−2.95, −0.79)
Race	
White vs. Black	3.70 (0.18, 5.64)
Other vs. White	−0.13 (−2.54, 2.28)
Other vs. Black	3.57 (0.45, 6.69)

RD (95% CI)

Figure 2. Risk differences for neuropsychiatric adverse events with varenicline, bupropion, NRT, and placebo

Period for ascertainment of neuropsychiatric adverse events was during 12 weeks' treatment and 30 days after last dose. Model terms included: treatment group (varenicline, bupropion, NRT, placebo), cohort (schizophrenia spectrum disorders no psychiatric disorders), treatment by cohort interaction, region (US or non-US), and race (White, Black, Other). CI, confidence interval; NRT, nicotine replacement therapy (transdermal nicotine patch); RD, risk difference.

Table 1

Baseline characteristics by treatment group and cohort

	Schizophrenia spectrum disorders subcohort					No psychiatric disorders cohort					
	All n=390	Varenicline n=95	Bupropion n=98	NRT n=99	Placebo n=98	All n=4,028	Varenicline n=1,005	Bupropion n=1,001	NRT n=1,013	Placebo n=1,009
	%	%	%	%	%	%	%	%	%	%
Demographic characteristics										
Female sex *	36	36	34	38	36	50	49	49	50	51
Age, years (M±SD)	44.5±10.6	44.6±11.6	44.5±10.7	43.3±10.2	45.4±9.8	45.9±12.9	45.8±12.9	46.0±13.0	46.1±12.8	45.9±12.8
Race *										
White	64	62	61	64	68	83	82	83	83	82
Black	32	35	37	31	27	13	14	12	13	13
Other	4	3	2	5	5	5	4	5	4	6
BMI *, kg/m² (M±SD)	29.8±6.9	30.6±7.5	29.6±7.0	29.3±6.6	29.5±6.6	27.6±6.1	27.4±6.0	27.6±6.2	27.8±6.3	27.8±6.0
Smoking characteristics										
FTCD score *a , (M±SD)	6.9±1.8	6.8±1.9	6.9±1.7	6.8±2.0	7.0±1.7	5.5±2.0	5.5±2.0	5.5±2.0	5.6±2.0	5.5±2.0
Cigarettes smoked per day in past month *, n (M±SD)	23.2±10.7	22.5±9.4	22.2±7.4	23.9±14.9	24.3±9.5	20.7±8.0	20.7±8.3	20.7±7.9	20.8±8.2	20.5±7.9
Previous quit attempts, n (M±SD)	2.4±4.0	2.2±3.2	1.9±2.0	2.2±2.8	3.3±6.4	3.2±9.7	3.2±13.7	3.3±10.2	3.2±5.1	3.1±7.4
Prior cessation aid trials										
Varenicline *	8	9	8	8	6	14	13	15	16	14
Bupropion *b ,	4	3	6	2	3	9	9	9	9	9
NRT *	15	18	13	12	17	25	22	26	25	25
Psychiatric characteristics										
Past alcohol use disorder	13	15	11	9	16	<1	<1	<1	0	<1
Past substance abuse disorder c	23	25	21	18	28	<1	<1	<1	0	<1
Suicidal ideation *d ,	29	26	29	31	28	5	5	4	5	5

	Schizophrenia spectrum disorders subcohort					No psychiatric disorders cohort				
	All n=390	Varenicline n=95	Bupropion n=98	NRT n=99	Placebo n=98	All n=4,028	Varenicline n=1,005	Bupropion n=1,001	NRT n=1,013	Placebo n=1,009
	%	%	%	%	%	%	%	%	%	%
Suicidal behavior*,[d]	18	16	20	22	15	<1	<1	<1	<1	<1
HADS score [e]										
Anxiety subscale score* (M±SD)	5.1±4.1	4.6±4.0	5.4±4.2	5.5±4.5	5.0±3.8	2.8±2.7	2.8±2.8	2.7±2.7	2.7±2.6	2.9±2.8
Depression subscale score* (M±SD)	3.9±3.2	4.0±3.6	4.2±2.8	3.8±3.3	3.8±3.0	1.5±2.1	1.5±2.1	1.4±2.0	1.5±2.0	1.6±2.1
BPAQ score*,[f] (M±SD)	62.7±20.1	61.7±19.8	63.4±20.3	63.8±20.7	61.6±19.7	52.2±15.4	52.4±15.5	51.9±15.3	52.2±15.6	52.3±15.4
Psychotropic medication*										
Antipsychotics	94	97	93	93	95	<1	<1	<1	<1	<1
First-generation	24	23	30	18	25	<1	<1	0	<1	<1
Second-generation	88	93	80	91	89	<1	<1	<1	0	<1
Clozapine	8	5	10	10	6	<1	0	0	0	<1
Antidepressants	31	32	28	36	25	3	2	2	3	4
Anxiolytics, hypnotics	17	19	17	21	11	6	5	5	6	6
Mood stabilizers	4	4	3	6	2	<1	<1	<1	<1	1

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; NRT, nicotine replacement therapy (transdermal nicotine patch); SD, standard deviation.

[a] Possible FTCD scores range from 0–10, with higher scores indicating more intense physical dependence on nicotine.

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

[c] Substance use disorder other than alcohol, caffeine or nicotine.

[d] Lifetime history of suicidal ideation or behavior from C-SSRS. Possible C-SSRS scores range from 2–25, with a higher number indicating more intense ideation and greater risk.

[e] Possible HADS scores range from 0–21 for either anxiety or depression, with higher scores indicating higher levels of either anxiety or depression.

[f] Possible BPAQ scores range from 29–145, with higher scores indicating higher levels of aggression.

* p<.001 for comparison of baseline variable by cohort.