Efficacy and Safety of Pharmacotherapeutic Smoking Cessation Aids in Schizophrenia Spectrum Disorders: Subgroup Analysis of EAGLES
[ONLINE SUPPLEMENT]

Data-sharing statement

Upon request, and subject to certain criteria, conditions, and exceptions (see https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information), Pfizer will provide access to individual de-identified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines, and medical devices: 1) for indications that have been approved in the USA and/or EU; or 2) in programs that have been terminated (i.e., development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The de-identified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.

Observed 7-day point prevalence abstinence at the end of treatment (week 12) according to baseline Clinical Global Impression – Severity score in the schizophrenia spectrum disorders subcohort

	CGI-S,[a] schizophrenia spectrum disorders subcohort (N=348)							
	Normal, not at all ill n=17		Borderline, mentally ill n=121		Mildly ill n=155		Moderately ill n=55	
	n	%	n	%	n	%	n	%
7-day PPA at week 12	6	35	18	15	23	15	12	22

CGI-S, Clinical Global Impression – Severity; PPA, point prevalence abstinence.
[a] Possible CGI-S scores range from 1–7 with higher scores indicating more severe illness.

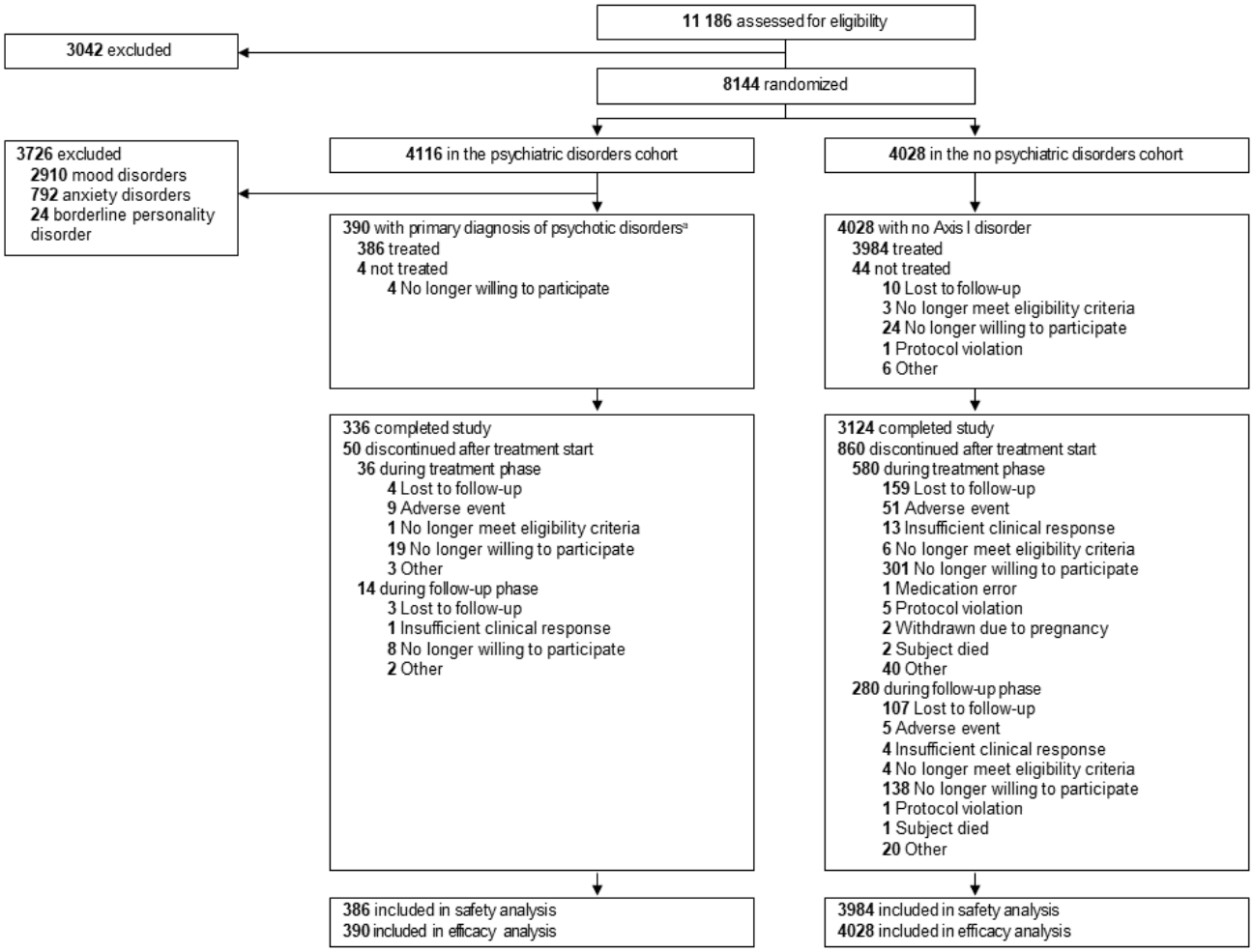
Incidence of moderate and severe neuropsychiatric adverse events among all treated participants

	Schizophrenia spectrum disorders subcohort					No psychiatric disorders cohort				
	All n=386	**Varenicline n=95**	**Bupropion n=96**	**NRT n=99**	**Placebo n=96**	**All n=3,984**	**Varenicline n=990**	**Bupropion n=989**	**NRT n=1,006**	**Placebo n=999**
	%	**%**	**%**	**%**	**%**	**%**	**%**	**%**	**%**	**%**
Primary composite neuropsychiatric adverse event endpoint										
Observed incidence	6	6	6	5	6	2	1	2	2	2
Estimated endpoint*	5	5	6	4	6	1	<1	1	2	2
95% CI	2.95–7.67	–.38–9.48	1.99–10.97	–.56–8.11	1.64–11.21	.61–2.08	–.78–1.41	.36–2.61	.91–3.21	.33–2.71
Observed components ≥1% in any treatment group*										
Anxiety	<1	0	0	1	0	<1	0	<1	0	<1
Depression	<1	1	0	0	1	<1	<1	0	0	0
Agitation	1	2	2	1	1	1	1	1	2	1
Aggression	1	2	0	0	2	<1	<1	<1	<1	<1
Delusions	<1	1	0	1	0	<1	0	0	<1	0
Hallucinations	1	2	2	1	0	<1	<1	0	0	0
Mania	<1	0	1	0	1	<1	0	<1	<1	<1
Panic	<1	0	1	1	0	<1	0	<1	<1	<1
Paranoia	<1	1	0	0	1	<1	0	<1	0	0
Psychosis	1	1	1	2	1	<1	0	0	<1	0

Suicidal ideation[a]	<1	0	1	1	0	<1	0	<1	<1	<1
Observed events of severe intensity only	1	1	0	2	1	<1	<1	<1	<1	<1
Observed components of severe intensity only and ≥1% in any treatment group										
Anxiety	<1	0	0	1	0	<1	0	<1	0	<1
Depression	<1	1	0	0	1	<1	<1	0	0	0
Events										
Serious adverse events	<1	1	0	1	0	<1	0	<1	<1	<1
Resulting in permanent treatment discontinuations	2	2	1	2	1	<1	<1	<1	<1	<1
Serious or severe adverse event, or leading to treatment discontinuations or interventions	2	2	1	2	2	<1	<1	<1	<1	1
C-SSRS[b]										
Suicidal ideation	2	1	2	2	3	<1	<1	<1	<1	<1
Suicidal behavior	<1	0	0	0	1	<1	0	<1	<1	<1

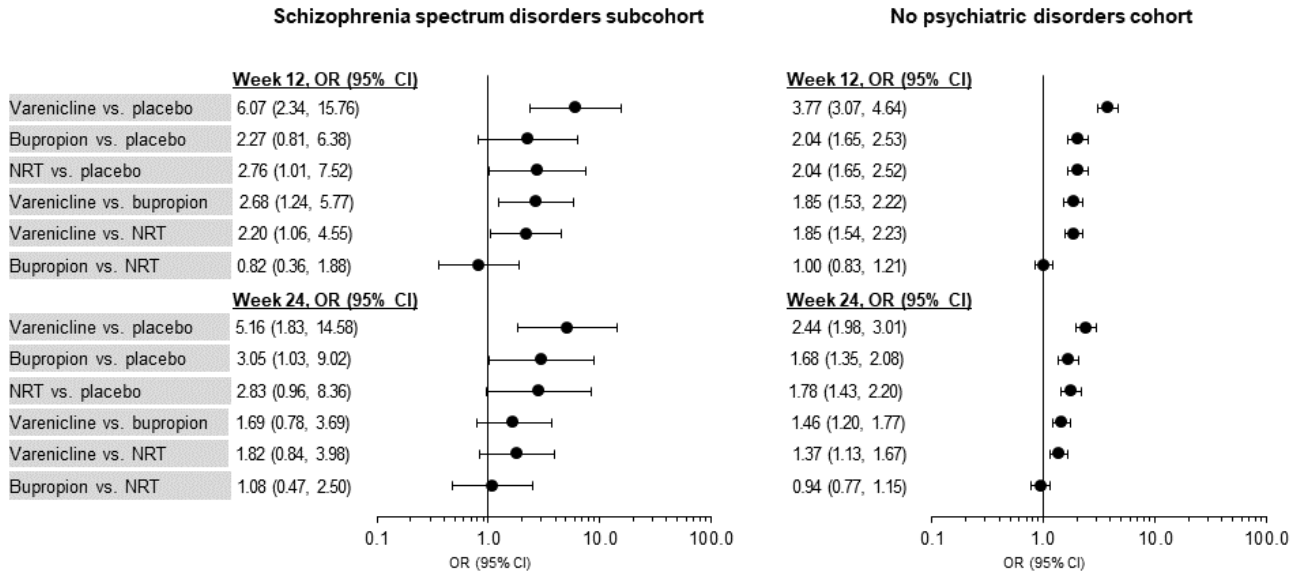
CI, confidence interval; C-SSRS, Columbia Suicide Severity Rating Scale NRT, nicotine replacement therapy.
[a] Incidence of suicide, suicidal behavior, feeling abnormal, homicidal ideation, hostility was <1% in any treatment group.
[b] Possible C-SSRS scores range from 2–25, with a higher number indicating more intense ideation and greater risk.
*****p<.001 for schizophrenia spectrum subcohort vs. no psychiatric disorders cohort.

Participant disposition (CONSORT)



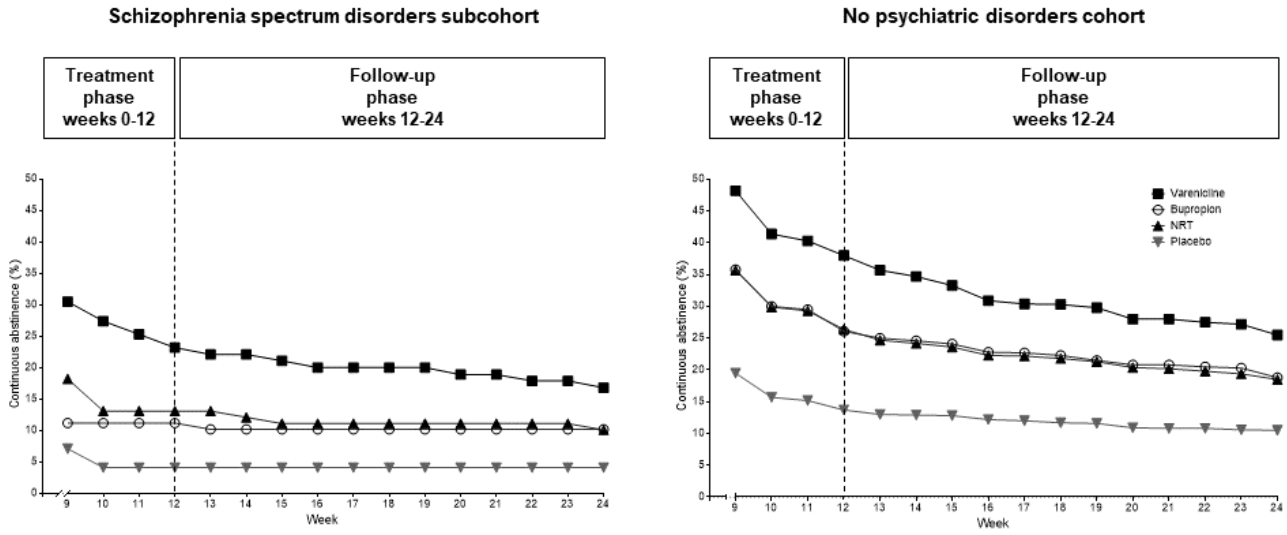
[a]Paranoid schizophrenia (n=261), schizoaffective disorder (n=87), residual schizophrenia (n=25), undifferentiated schizophrenia (n=13), disorganized schizophrenia (n=3), and catatonic schizophrenia (n=1).

Treatment comparisons for 7-day point prevalence abstinence at end of treatment (week 12) and end of follow-up (week 24)



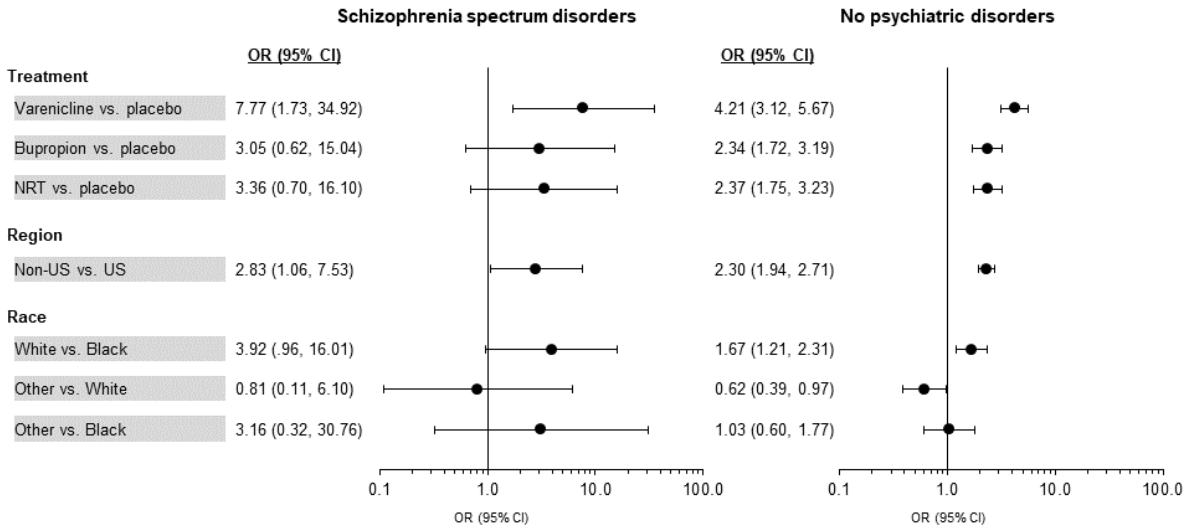
For treatment comparisons, treatment group (varenicline, bupropion, NRT, placebo), cohort (schizophrenia spectrum disorders, no psychiatric disorders), treatment by cohort interaction, region (US or non-US), and region by cohort interaction were included in the model.
CI, confidence interval; NRT, nicotine replacement therapy (transdermal nicotine patch); OR, odds ratio.

Observed continuous abstinence rates at each study visit in those with schizophrenia spectrum disorders



NRT, nicotine replacement therapy (transdermal nicotine patch).

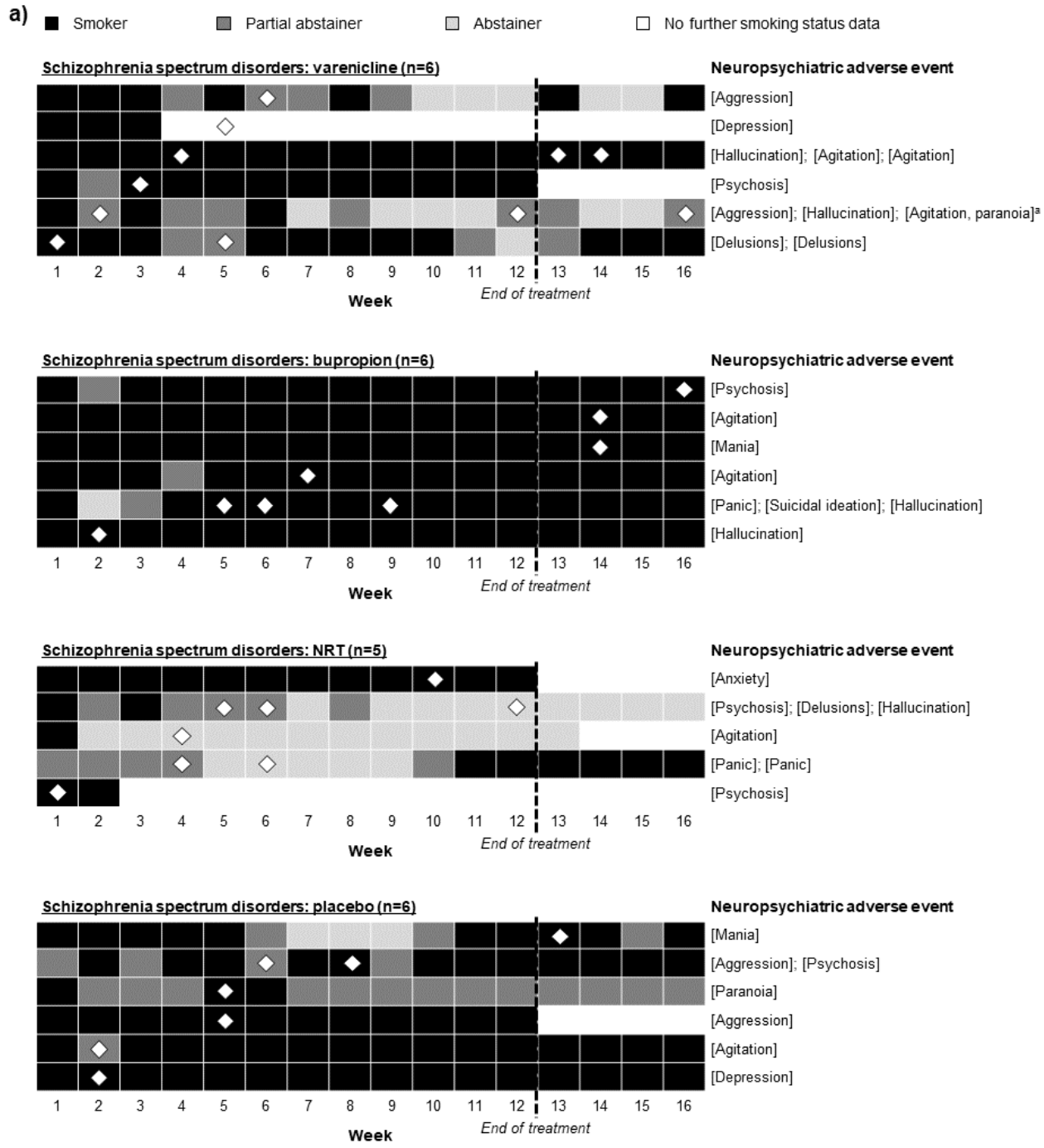
Odds ratios for continuous abstinence for weeks 9–12 for variables included in the model

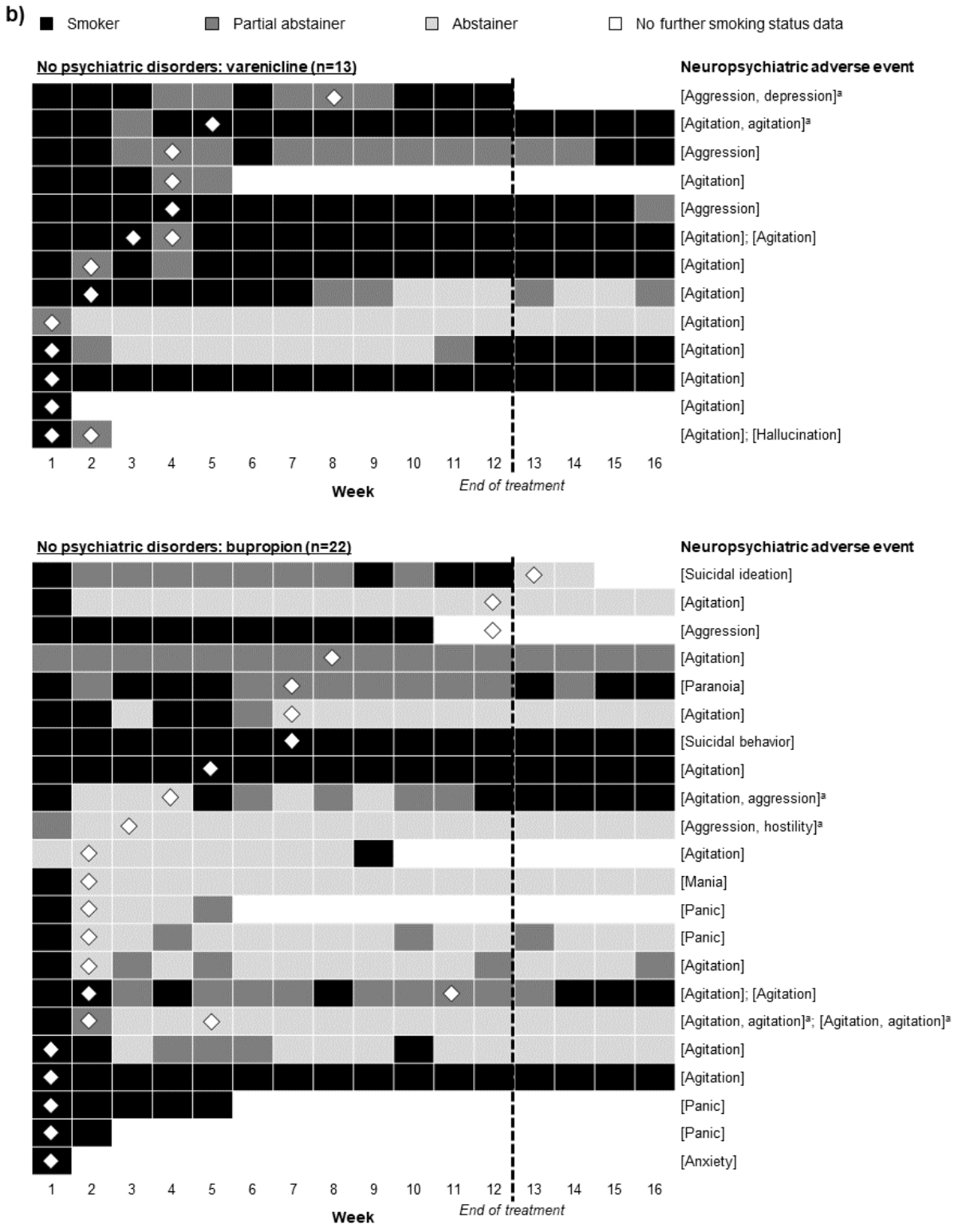


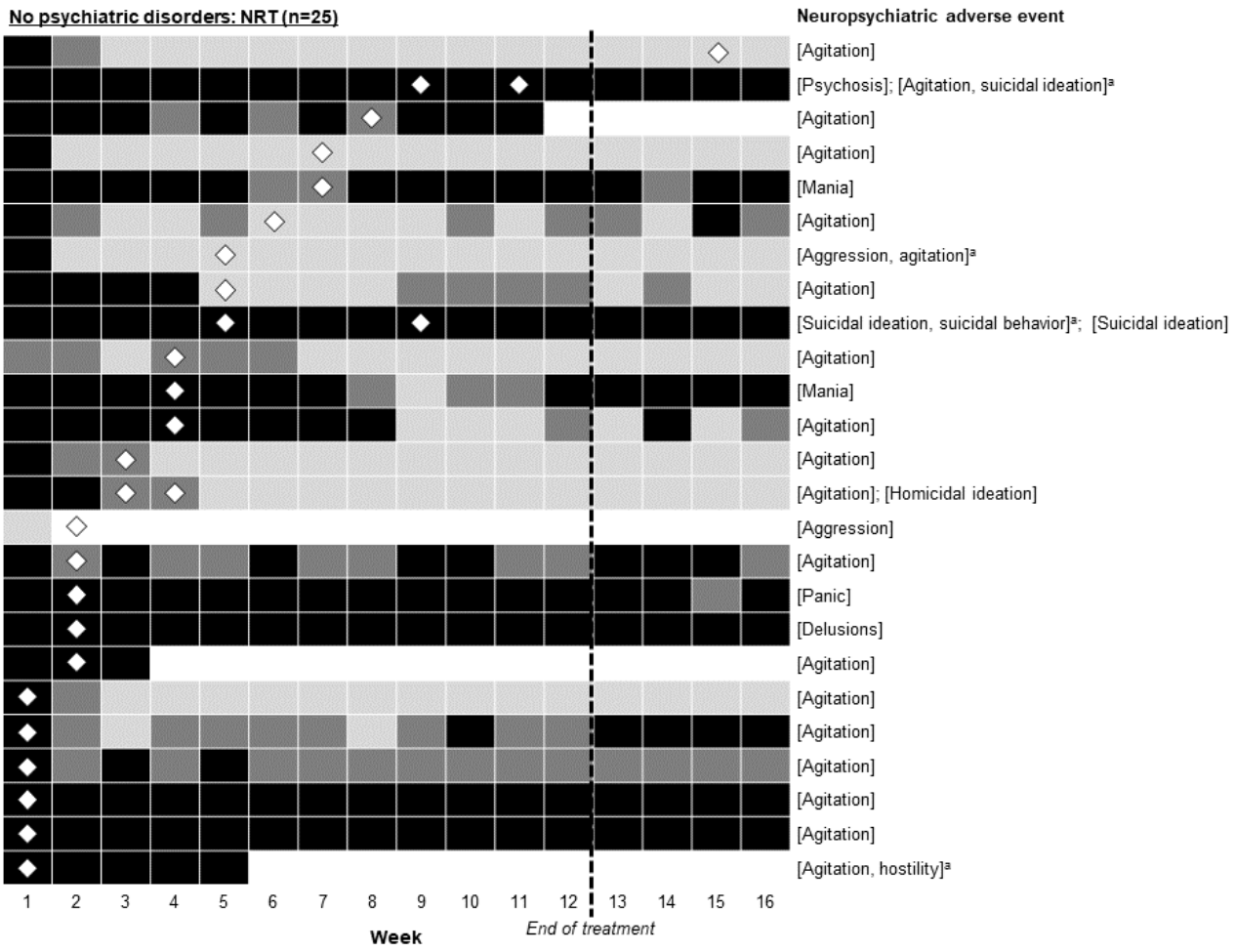
Model terms included: treatment group (varenicline, bupropion, NRT, placebo), cohort (schizophrenia spectrum disorders, no psychiatric disorders), treatment by cohort interaction, region (US, non-US), race (White, Black, Other), age, BMI, FTCD score, cigarettes per day in the past month, and duration of smoking.

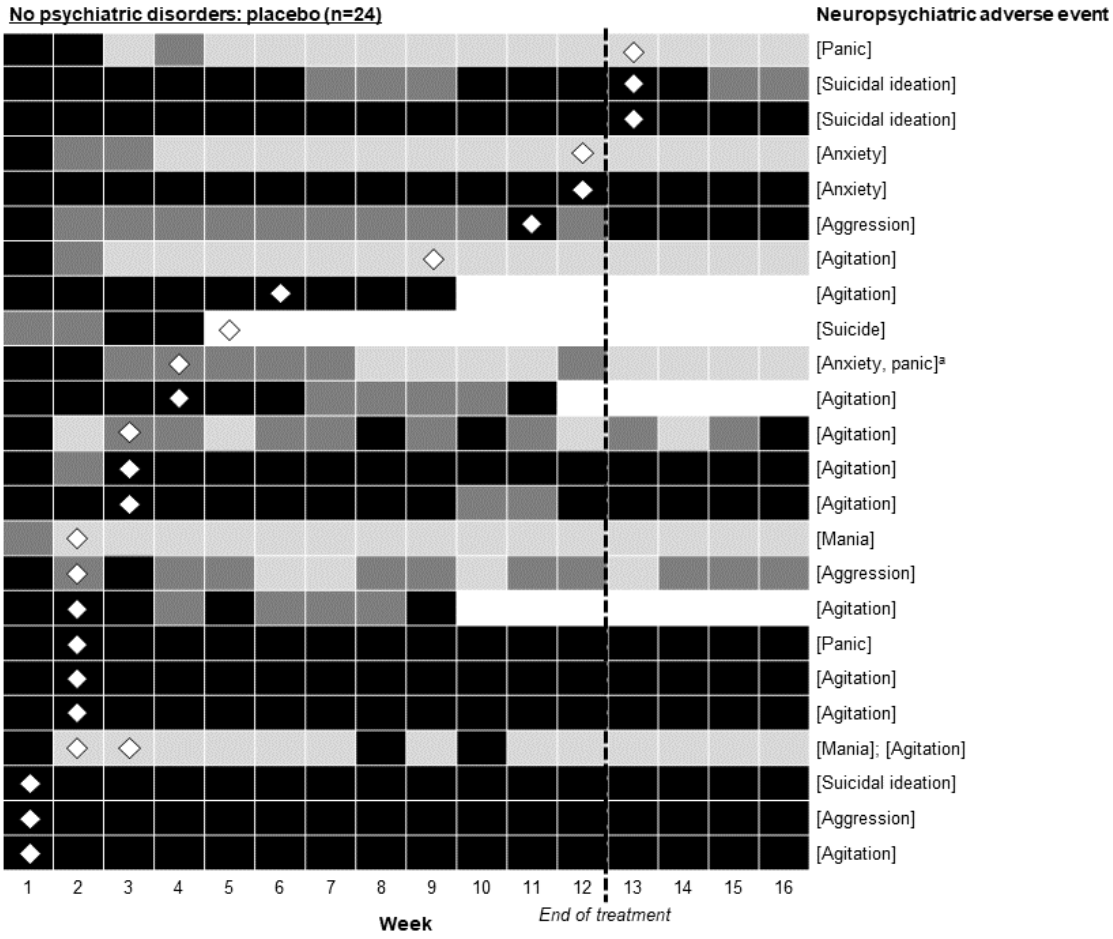
BMI, body mass index; CI, confidence interval; FTCD, Fagerström Test for Cigarette Dependence; NRT, nicotine replacement therapy (transdermal nicotine patch); OR, odds ratio.

Treatment-emergent neuropsychiatric adverse events in relation to 7-day point prevalence abstinence status with varenicline, bupropion, NRT, and placebo in a) the schizophrenia spectrum disorders subcohort and b) the no psychiatric disorders cohort




b)
Smoker
Partial abstainer
Abstainer
No further smoking status data
No psychiatric disorders: varenicline (n=13)
Neuropsychiatric adverse event
[Aggression, depression]a
[Agitation, agitation]a
[Aggression]
[Agitation]
[Aggression]
[Agitation]; [Agitation]
[Agitation]
[Agitation]
[Agitation]
[Agitation]
[Agitation]
[Agitation]
[Agitation]; [Hallucination]
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
Week
End of treatment
No psychiatric disorders: bupropion (n=22)
Neuropsychiatric adverse event
[Suicidal ideation]
[Agitation]
[Aggression]
[Agitation]
[Paranoia]
[Agitation]
[Suicidal behavior]
[Agitation]
[Agitation, aggression]a
[Aggression, hostility]a
[Agitation]
[Mania]
[Panic]
[Panic]
[Agitation]
[Agitation]; [Agitation]
[Agitation, agitation]a; [Agitation, agitation]a
[Agitation]
[Agitation]
[Panic]
[Panic]
[Anxiety]
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
Week
End of treatment


No psychiatric disorders: NRT (n=25)
Neuropsychiatric adverse event
[Agitation]
[Psychosis]; [Agitation, suicidal ideation]a
[Agitation]
[Agitation]
[Mania]
[Agitation]
[Aggression, agitation]a
[Agitation]
[Suicidal ideation, suicidal behavior]a; [Suicidal ideation]
[Agitation]
[Mania]
[Agitation]
[Agitation]
[Agitation]; [Homicidal ideation]
[Aggression]
[Agitation]
[Panic]
[Delusions]
[Agitation]
[Agitation]
[Agitation]
[Agitation]
[Agitation]
[Agitation, hostility]a
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
Week
End of treatment



Period for ascertainment of neuropsychiatric adverse events was during 12 weeks of treatment and ≤30 days after last dose. Each row represents an individual participant who experienced a moderate to severe neuropsychiatric adverse event; a white diamond indicates the week in which the neuropsychiatric adverse event occurred. Study medication was initiated in week 1.

Abstainer was defined as self-report of no cigarettes in the past 7 days and expired carbon monoxide ≤10 parts per million at that visit; partial abstainer was defined as abstinent for >2 days in the past 7 days; smoker was defined as smoking for the past 7 days.

NRT, nicotine replacement therapy (transdermal nicotine patch).

[a] Multiple neuropsychiatric adverse events recorded at clinic visit.