Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders (EAGLES): a double-blind, randomised, placebo-controlled clinical trial

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Summary

Background Substantial concerns have been raised about the neuropsychiatric safety of the smoking cessation medications varenicline and bupropion. Their efficacy relative to nicotine patch largely relies on indirect comparisons, and there is limited information on safety and efficacy in smokers with psychiatric disorders. We compared the relative neuropsychiatric safety risk and efficacy of varenicline and bupropion with nicotine patch and placebo in smokers with and without psychiatric disorders.

Methods We did a randomised, double-blind, triple-dummy, placebo-controlled and active-controlled (nicotine patch; 21 mg per day with taper) trial of varenicline (1 mg twice a day) and bupropion (150 mg twice a day) for 12 weeks with 12-week non-treatment follow-up done at 140 centres (clinical trial centres, academic centres, and outpatient clinics) in 16 countries between Nov 30, 2011, and Jan 13, 2015. Participants were motivated-to-quit smokers with and without psychiatric disorders who received brief cessation counselling at each visit. Randomisation was computer generated (1:1:1:1 ratio). Participants, investigators, and research personnel were masked to treatment assignments. The primary endpoint was the incidence of a composite measure of moderate and severe neuropsychiatric adverse events. The main efficacy endpoint was biochemically confirmed continuous abstinence for weeks 9–12. All participants randomly assigned were included in the efficacy analysis and those who received treatment were included in the safety analysis. The trial is registered at ClinicalTrials.gov (number NCT01456936) and is now closed.

Findings 8144 participants were randomly assigned, 4116 to the psychiatric cohort (4074 included in the safety analysis) and 4028 to the non-psychiatric cohort (3984 included in the safety analysis). In the non-psychiatric cohort, 13 (1·3%) of 990 participants reported moderate and severe neuropsychiatric adverse events in the varenicline group, 22 (2·2%) of 989 in the bupropion group, 25 (2·5%) of 1006 in the nicotine patch group, and 24 (2·4%) of 999 in the placebo group. The varenicline–placebo and bupropion–placebo risk differences (RDs) for moderate and severe neuropsychiatric adverse events were –1·28 (95% CI –2·40 to –0·15) and –0·08 (–1·37 to 1·21), respectively; the RDs for comparisons with nicotine patch were –1·07 (–2·21 to 0·08) and 0·13 (–1·19 to 1·45), respectively. In the psychiatric cohort, moderate and severe neuropsychiatric adverse events were reported in 67 (6·5%) of 1026 participants in the varenicline group, 68 (6·7%) of 1017 in the bupropion group, 53 (5·2%) of 1016 in the nicotine patch group, and 50 (4·9%) of 1015 in the placebo group. The varenicline–placebo and bupropion–placebo RDs were 1·59 (95% CI –0·42 to 3·59) and 1·78 (–0·24 to 3·81), respectively; the RDs versus nicotine patch were 1·22 (–0·81 to 3·25) and 1·42 (–0·63 to 3·46), respectively. Varenicline-treated participants achieved higher abstinence rates than those on placebo (odds ratio [OR] 3·61, 95% CI 3·07 to 4·24), nicotine patch (1·68, 1·46 to 1·93), and bupropion (1·75, 1·52 to 2·01). Those on bupropion and nicotine patch achieved higher abstinence rates than those on placebo (OR 2·07 [1·75 to 2·45] and 2·15 [1·82 to 2·54], respectively). Across cohorts, the most frequent adverse events by treatment group were nausea (varenicline, 25% [511 of 2016 participants]), insomnia (bupropion, 12% [245 of 2006 participants]), abnormal dreams (nicotine patch, 12% [251 of 2022 participants]), and headache (placebo, 10% [199 of 2014 participants]). Efficacy treatment comparison did not differ by cohort.

Interpretation The study did not show a significant increase in neuropsychiatric adverse events attributable to varenicline or bupropion relative to nicotine patch or placebo. Varenicline was more effective than placebo, nicotine patch, and bupropion in helping smokers achieve abstinence, whereas bupropion and nicotine patch were more effective than placebo.

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Research in context

Evidence before this study

We searched PubMed, Cochrane Database of Systematic Reviews, and the websites of the US Food and Drug Administration (FDA) and European Medicines Agency for relevant reports published up to March 26, 2016, and reviewed the reference lists from these documents. There were no language restrictions and the search terms included "varenicline", "bupropion", "nicotine replacement therapy", "safety", "adverse events", and "suicide". Case reports and analyses of post-marketing pharmacovigilance data from Europe, the USA, and other countries detected a possible signal that varenicline use might be associated with neuropsychiatric adverse events, a concern that was eventually extended to use of bupropion. As a result, the FDA issued a post-marketing requirement to the makers of varenicline and bupropion to do a randomised controlled trial to assess the risk of serious neuropsychiatric adverse events.

By contrast, studies by various authors with a variety of control groups, in a broad range of study populations—some with very large sample sizes—did not detect any significant increase in neuropsychiatric adverse events in smokers prescribed varenicline or bupropion compared with nicotine replacement therapy or placebo. Although the results of these controlled studies consistently showed varenicline and bupropion to be associated with no greater incidence of serious neuropsychiatric adverse events than active or placebo comparators, some of the studies excluded smokers with psychiatric illness, a group who smoke a large proportion of the cigarettes consumed worldwide, and who might be more vulnerable to neuropsychiatric adverse events.

From the smoking cessation efficacy perspective, most data on the comparative efficacy of varenicline versus nicotine replacement therapy—such as those summarised in Cochrane network meta-analyses finding varenicline superior to single formulation nicotine replacement therapy—rely on indirect comparisons. A recent open-label trial comparing varenicline with single formulation and combination nicotine replacement therapy did not detect significant differences across the treatments at 26 weeks. No previous studies have compared the smoking cessation efficacy of the three first-line smoking cessation aids head-to-head in smokers, and none have done so in smokers with current or past psychiatric disorders.

Added value of this study

This study addresses the need for a prospective study of adequate size and rigour to assess the potential for varenicline and bupropion to cause serious neuropsychiatric adverse events. The findings show that it is highly unlikely that varenicline and bupropion contribute to neuropsychiatric adverse events of moderate-to-severe intensity at a rate above 1·5% in smokers without a psychiatric disorder and above 4% in smokers with such disorders. The results are also consistent with no increase in the incidence of these events. The study also provides the first definitive evidence on the relative effectiveness of the different smoking cessation medications in the special population of smokers with psychiatric disorders. The fact that the odds ratios for efficacy did not differ as a function of psychiatric status is crucial new information when it comes to treating this population who smoke at rates two to three times that of the general population and who are disproportionately affected by smoking-related illness. The findings will be used by medicines regulators, clinicians, and smokers to make an informed choice about life-preserving treatments.

Implications of all the available evidence

The findings from this study, the largest of its kind, together with those from meta-analyses of previous randomised controlled trials and very large observational cohort studies, make it highly unlikely that varenicline or bupropion increase the risk of moderate-to-severe neuropsychiatric adverse events in smokers without psychiatric disorders. The evidence from all available sources is less clear in smokers with psychiatric disorders; however, if there is an increased risk in this group, this is expected to be small.

The available evidence, substantially boosted by this study, clearly shows the efficacy of all three first-line smoking cessation medications with varenicline having the largest effect, in smokers with and without psychiatric disorders.

Introduction

The prescription medications varenicline and bupropion have been shown to substantially improve smokers' chances of stopping long term in many randomised trials and real-world observational studies.[1] However, substantial concerns have been raised about their safety, particularly with regard to neuropsychiatric adverse events such as suicidality and aggression.[2] Meta-analyses of randomised trials and large comparative observational studies have not supported these safety concerns, but before that information became available the US Food and Drug Administration (FDA) required the makers of these medications to conduct a sufficiently large randomised trial to provide greater clarity on their potential safety risks.[3] Additionally, the smoking cessation efficacy of these medications relative to each other and to nicotine replacement therapy, especially in smokers with psychiatric disorders, remains uncertain, depending largely on indirect comparisons and a limited number of studies with relatively small sample sizes.[4] The present study sought to address these issues with a very large double-blind, triple-dummy, active-controlled and placebo-controlled, randomised trial in smokers with and without a psychiatric disorder. The issue is of crucial importance because of the urgency surrounding smoking cessation, particularly for smokers with respiratory, cardiovascular, or other smoking-related diseases, and the need to be able to provide maximum

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support for smokers to help them achieve abstinence based on an accurate risk–benefit analysis.

Clinical practice guidelines recommend that the most effective way for moderate-to-heavy smokers to quit is by combining a smoking cessation medication with counselling.[4] However, smoking cessation support is underused,[5] in part due to smokers' and clinicians' concerns that the medications might not be safe, especially regarding the risk of developing serious neuropsychiatric symptoms—a concern that is reflected in the package insert for two of the first-line agents, varenicline and bupropion, as warnings or precautions in most countries and as boxed warnings in some countries including the USA. Given the high risk of smoking-induced illness and death, the reluctance of clinicians to prescribe the most effective smoking cessation medications places many smokers at further risk.

Concerns about neuropsychiatric safety of varenicline and bupropion arose from case reports,[6,7] post-marketing surveillance analyses,[2,8] and the initial dearth of studies in smokers with psychiatric disorders who are most likely to report such events.[9] However, studies with active and placebo comparators published over the past 4 years report that use of these medications did not increase neuropsychiatric symptom risk. Randomised, placebo-controlled trials of varenicline in smokers with various psychiatric disorders[10,11] identified no neuropsychiatric safety signals and no worsening of the underlying psychiatric condition. Independent meta-analyses of these trials have reported no evidence of an association between varenicline[12,13] or bupropion[14] and neuropsychiatric adverse events. Observational studies examining severe outcomes (eg, suicidal behaviour, admission to hospital) in large cohorts of smokers, many of whom had comorbid psychiatric disorders, have not found a heightened risk of serious neuropsychiatric adverse events for varenicline[9,15] or bupropion.[16] However, these studies all have limitations.[3] For example, most studies included in the meta-analyses did not prospectively and systematically probe for all serious neuropsychiatric adverse events of interest, and the more recent observational studies might suffer from channelling bias where sicker patients were shunted away from using the non-nicotine smoking cessation aids because of concerns about their side-effects.[3] Thus, there remains a need to determine the neuropsychiatric safety profile of varenicline and bupropion in a randomised, double-blind, active-controlled and placebo-controlled trial in smokers with and without psychiatric disorders that systematically probes for these neuropsychiatric adverse events while participants are on-treatment and off-treatment during and following their smoking cessation attempt.

In addition to safety issues, the smoking cessation efficacy of the non-nicotine medications relative to nicotine replacement therapy, which also plays a role in determining their benefit–risk ratio, has also not been well studied in head-to-head trials, particularly in smokers with psychiatric disorders. A network meta-analysis done by the independent Cochrane Database of Systematic Reviews recommended that direct comparisons among single and combination formulations of nicotine replacement therapy with varenicline would be valuable.[1] A recent open-label trial in lighter smokers[17] further highlights the need for double-blind, placebo-controlled, head-to-head comparisons as evidenced by that study's results being inconsistent with previous findings of meta-analyses that varenicline was more efficacious than single formulation nicotine replacement therapy.[1] It is also not known whether the relative efficacies of these first-line smoking cessation medications differ as a function of a smoker's psychiatric history, because no previous comparative efficacy trials directly compared the medications in smokers with and without psychiatric disorders.

With these gaps in the literature in mind, herein we describe the results of the largest trial of pharmacotherapy for smoking cessation done to date, with the objective of comparing the relative safety and efficacy of these medications in smokers with and without psychiatric disorders. The study was requested by, and designed in consultation with, the FDA. The study is also a post-authorisation safety study in the European Union.

Methods

Study design and participants

The Evaluating Adverse Events in a Global Smoking Cessation Study (EAGLES) was a multinational, multicentre, randomised, double-blind, placebo-controlled and active-controlled trial, done at 140 centres in 16 countries across five continents (appendix). Study sites included clinical trial centres, academic centres, and outpatient clinics treating patients with and without psychiatric disorders.

See Online for appendix

Eligible participants were smokers, aged 18–75 years, with and without prespecified psychiatric diagnoses per the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR),[18] who smoked an average of ten or more cigarettes per day during the previous year, had an exhaled carbon monoxide concentration greater than 10 parts per million (ppm) at screening, and who were motivated to stop smoking as evidenced by signing the informed consent before trial enrolment specifying that a target quit date would be set. Potential participants were recruited from the investigators' own clinics; through newspaper, radio, and television advertising; and fliers and posters. Participants were included in the psychiatric cohort if they met DSM-IV-TR diagnostic criteria for mood disorders including major depressive disorder or bipolar disorder; anxiety disorders including panic disorder, with or without agoraphobia, post-traumatic stress disorder, obsessive-compulsive disorder, social phobia, and generalised anxiety disorder; psychotic disorders including schizophrenia and schizoaffective disorders;

	Non-psychiatric cohort* (n=3984)				Psychiatric cohort* (n=4074)			
	Varenicline (n=990)	Bupropion (n=989)	Nicotine patch (n=1006)	Placebo (n=999)	Varenicline (n=1026)	Bupropion (n=1017)	Nicotine patch (n=1016)	Placebo (n=1015)
Demographic characteristics								
Sex								
Male	510 (52%)	503 (51%)	497 (49%)	489 (49%)	392 (38%)	387 (38%)	384 (38%)	387 (38%)
Female	480 (48%)	486 (49%)	509 (51%)	510 (51%)	634 (62%)	630 (62%)	632 (62%)	628 (62%)
Age (years)	45·8 (13·0)	46·0 (13·0)	46·1 (12·8)	45·9 (12·8)	47·2 (11·8)	46·7 (12·2)	47·6 (11·5)	46·9 (11·5)
Race								
White	819 (83%)	820 (83%)	837 (83%)	817 (82%)	849 (83%)	816 (80%)	804 (79%)	822 (81%)
Black	135 (14%)	116 (12%)	127 (13%)	126 (13%)	145 (14%)	165 (16%)	176 (17%)	155 (15%)
Asian	14 (1%)	16 (2%)	13 (1%)	19 (2%)	5 (<1%)	10 (1%)	11 (1%)	7 (1%)
Other	22 (2%)	37 (4%)	29 (3%)	37 (4%)	27 (3%)	26 (3%)	25 (2%)	30 (3%)
Unspecified	0	0	0	0	0	0	0	1 (<1%)
Weight (kg)	80·0 (19·5)	80·4 (20·1)	81·6 (19·6)	80·6 (19·3)	83·0 (21·5)	82·5 (21·3)	80·8 (20·1)	82·7 (21·3)
Region								
USA	464 (47%)	466 (47%)	476 (47%)	469 (47%)	590 (58%)	586 (58%)	575 (57%)	581 (57%)
Western Europe and other countries†	322 (33%)	320 (32%)	322 (32%)	326 (33%)	297 (29%)	292 (29%)	303 (30%)	297 (29%)
Eastern Europe‡	111 (11%)	112 (11%)	112 (11%)	111 (11%)	94 (9%)	92 (9%)	93 (9%)	93 (9%)
South and Middle America§	93 (9%)	91 (9%)	96 (10%)	93 (9%)	45 (4%)	47 (5%)	45 (4%)	44 (4%)
Smoking characteristics								
FTCD score	5·5 (2·0)	5·5 (2·0)	5·6 (2·0)	5·5 (2·0)	6·0 (1·9)	6·1 (1·9)	6·0 (2·0)	5·9 (2·0)
Duration of smoking (years)	27·8 (12·8)	28·2 (13·0)	28·2 (12·8)	28·2 (12·6)	28·9 (11·8)	28·2 (12·4)	28·9 (11·9)	28·3 (11·6)
Cigarettes smoked per day in past month	20·8 (8·3)	20·6 (7·8)	20·8 (8·2)	20·5 (7·9)	20·6 (8·0)	20·5 (8·2)	20·8 (9·1)	20·7 (8·2)
Previous quit attempts	3·3 (13·8)	3·4 (10·3)	3·1 (4·2)	3·2 (7·4)	3·4 (7·7)	3·5 (6·9)	3·3 (5·3)	3·6 (10·9)
Participants with at least one previous quit attempt	809 (82%)	808 (82%)	832 (83%)	795 (80%)	855 (83%)	843 (83%)	851 (84%)	854 (84%)
Psychiatric characteristics								
Primary diagnosis, SCID								
Unipolar and bipolar mood disorders	..	..	..	..	731 (71%)	716 (70%)	713 (70%)	722 (71%)
Anxiety disorders	..	..	..	..	193 (19%)	200 (20%)	195 (19%)	194 (19%)
Psychotic disorders	..	..	..	..	95 (9%)	96 (9%)	99 (10%)	96 (9%)
Personality disorders	..	..	..	..	7 (1%)	5 (<1%)	9 (1%)	3 (<1%)
HADS								
Total score	4·4 (4·4, 0–28)	4·1 (4·1, 0–24)	4·2 (4·1, 0–25)	4·5 (4·3, 0–22)	8·3 (6·5, 0–30)	8·7 (6·9, 0–36)	8·4 (6·6, 0–31)	8·2 (6·2, 0–36)
Anxiety subscale score	2·8 (2·8)	2·7 (2·6)	2·7 (2·6)	2·9 (2·8)	5·1 (3·8)	5·3 (4·0)	5·2 (4·0)	5·2 (3·8)
Depression subscale score	1·6 (2·1)	1·4 (2·0)	1·5 (2·0)	1·6 (2·1)	3·2 (3·3)	3·4 (3·5)	3·2 (3·3)	3·1 (3·2)
Lifetime suicide-related history from C-SSRS								
Ideation	48 (5%)	43 (4%)	50 (5%)	49 (5%)	338 (33%)	357 (35%)	333 (33%)	349 (34%)
Behaviour	6 (1%)	9 (1%)	7 (1%)	6 (1%)	137 (13%)	143 (14%)	111 (11%)	123 (12%)
Receiving psychotropic medication at enrolment	75 (8%)	72 (7%)	85 (8%)	96 (10%)	534 (52%)	471 (46%)	491 (48%)	500 (49%)
Antidepressants	22 (2%)	21 (2%)	26 (3%)	36 (4%)	384 (37%)	318 (31%)	334 (33%)	341 (34%)
Anxiolytics, hypnotics, and other sedatives	53 (5%)	49 (5%)	61 (6%)	61 (6%)	160 (16%)	141 (14%)	186 (18%)	136 (13%)
Antipsychotics	2 (<1%)	2 (<1%)	2 (<1%)	7 (1%)	165 (16%)	160 (16%)	167 (16%)	159 (16%)
Mood stabilisers	6 (1%)	1 (<1%)	3 (<1%)	10 (1%)	16 (2%)	22 (2%)	22 (2%)	22 (2%)
Other¶	1 (<1%)	2 (<1%)	3 (<1%)	0	1 (<1%)	6 (1%)	1 (<1%)	3 (<1%)

Data are mean (SD), mean (SD, range), or n (%), unless otherwise stated. C-SSRS=Columbia-Suicide Severity Rating Scale. FTCD=Fagerström Test for Cigarette Dependence. ..=not applicable. HADS=Hospital Anxiety and Depression Scale. SCID=Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Axis I or II Disorders. *All-treated population. †Australia, Canada, Denmark, Finland, Germany, New Zealand, South Africa, and Spain. ‡Bulgaria, Russia, and Slovakia. §Argentina, Brazil, Chile, and Mexico. ¶Psychostimulants, aminoacids, and herbals or botanicals.

Table 1: **Baseline characteristics**

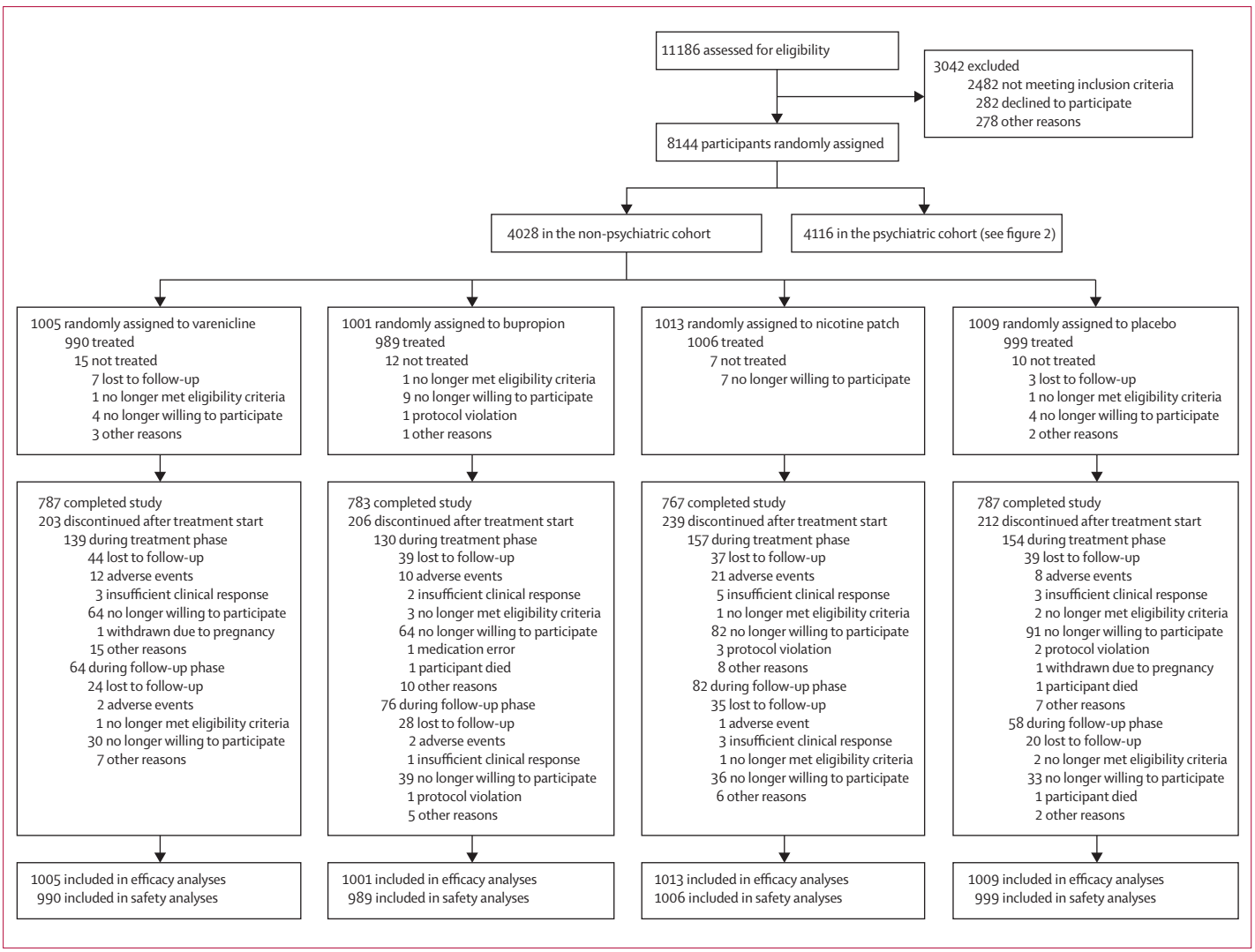


Figure 1: **Trial profile: non-psychiatric cohort**

or borderline personality disorder. Those with qualifying primary psychiatric disorders were not excluded for other psychiatric comorbidities, but those secondary allowable diagnoses were also prespecified and excluded destabilising psychiatric conditions such as alcohol and other drug use disorders within the previous 12 months. Participants had to be considered clinically stable for inclusion (ie, no exacerbations of their condition in the preceding 6 months; on stable treatment for at least 3 months, with no treatment change anticipated during the study), and considered by the investigator not to be at high risk of self-injury or suicidal behaviour as gauged by participants' responses on the Suicide Behaviors Questionnaire—Revised,[19] or Columbia-Suicide Severity Rating Scale (C-SSRS),[20] both administered at screening, and, if necessary, professional mental health assessment. Participants in the non-psychiatric cohort had no confirmed history of DSM-IV-TR Axis I or II disorders. Complete inclusion and exclusion criteria are described in the appendix.

Written consent forms and study procedures were approved by the institutional review boards or ethics committees at participating institutions. The study adhered to the Declaration of Helsinki[21] and the International Conference on Harmonisation Good Clinical Practice Guidelines.[22] An independent Data Monitoring Committee reviewed safety data at prespecified timepoints to ensure participant safety and sample size adequacy. All participants signed informed consent and received financial compensation for study participation time and travel expenses as per standards set at each trial site.

Randomisation and masking

Eligible participants were stratified into a non-psychiatric cohort and four sub-cohorts in the psychiatric cohort based on their psychiatric primary diagnosis, and by site

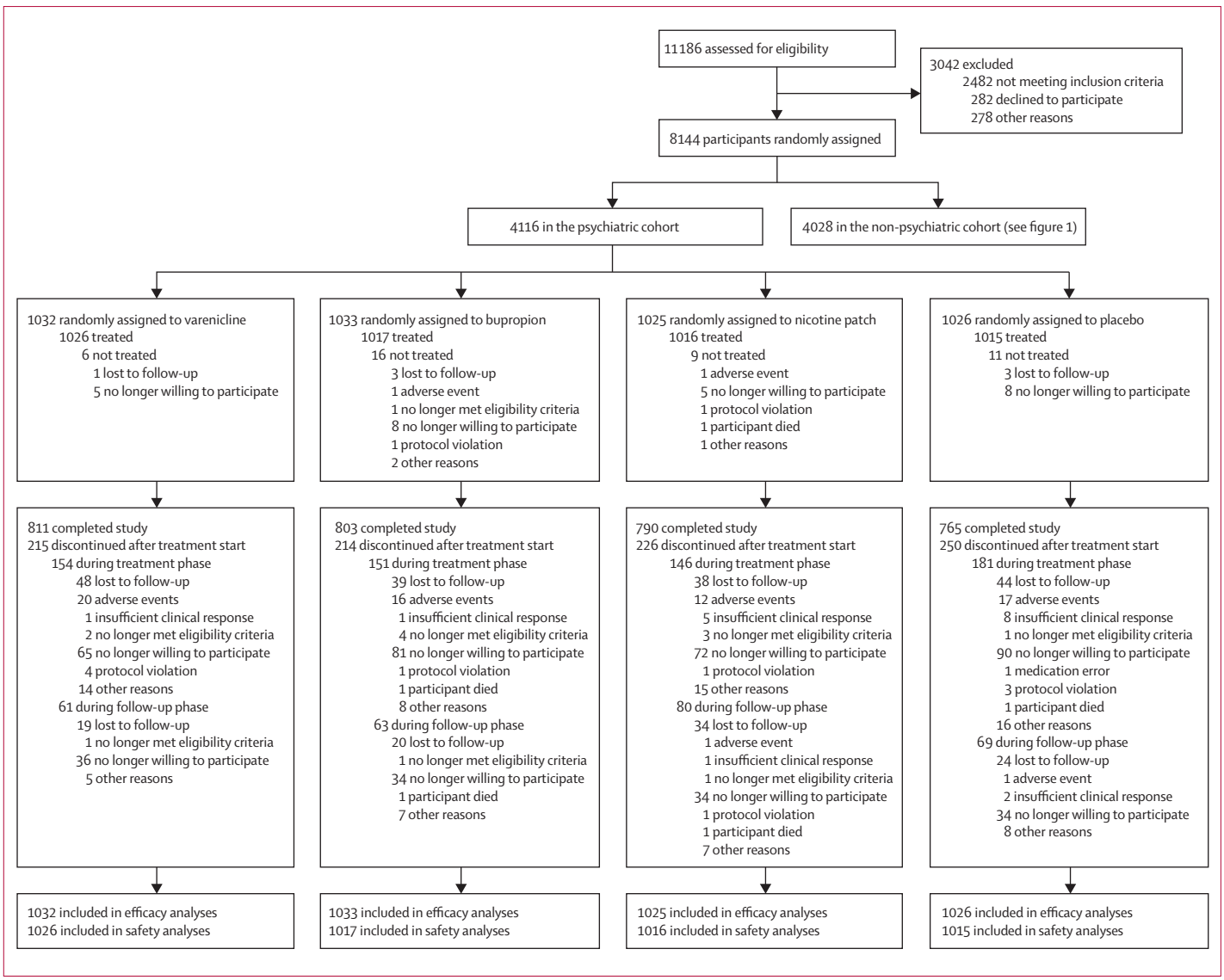


Figure 2: **Trial profile: psychiatric cohort**

region based on four prespecified geographical groups (table 1). Within this stratification, participants were then randomised to receive maximal target dosages of varenicline 1 mg twice a day, bupropion sustained release 150 mg twice a day, transdermal nicotine patch 21 mg per day with taper, or placebo (1:1:1:1 ratio) in a triple-dummy design for a 12-week treatment phase followed by a 12-week non-treatment phase (appendix). Participants were asked to complete up to 15 face-to-face visits and 11 telephone visits during the 24-week trial. The triple-dummy design feature required participants to take study medications as masked tablets dispensed in separate varenicline and bupropion pill bottles each with matching placebo along with either applying active or placebo patches on a daily basis. All participants received active treatment or placebo for each of the three medication conditions and were instructed to use all three of the treatments each day during the active treatment phase. Overall enrolment was to be equal (n=4000; 1000 per treatment group) for the two cohorts. Treatment groups were balanced across the five diagnostic groups (non-psychiatric cohort, psychiatric cohort mood, psychiatric cohort anxiety, psychiatric cohort psychotic, and psychiatric cohort personality disorders) for each of the four regions. A randomisation administrator, independent from the clinical study team, prepared the computer-generated randomisation schedule used to assign participants to treatment using a block size of 8 (1:1:1:1 ratio) for each of the 20 diagnosis by region combinations. Investigators obtained participant identification numbers via a web-based or telephone call-in drug management system. Study

	Non-psychiatric cohort* (n=3984)				Psychiatric cohort* (n=4074)			
	Varenicline (n=990)	Bupropion (n=989)	Nicotine patch (n=1006)	Placebo (n=999)	Varenicline (n=1026)	Bupropion (n=1017)	Nicotine patch (n=1016)	Placebo (n=1015)
Primary composite neuropsychiatric endpoint	13 (1·3%)	22 (2·2%)	25 (2·5%)	24 (2·4%)	67 (6·5%)	68 (6·7%)	53 (5·2%)†	50 (4·9%)
Estimated primary composite neuropsychiatric adverse events (% [95% CI])	1·25% (0·60 to 1·90)	2·44% (1·52 to 3·36)	2·31% (1·37 to 3·25)	2·52% (1·58 to 3·46)	6·42% (4·91 to 7·93)	6·62% (5·09 to 8·15)	5·20% (3·84 to 6·56)	4·83% (3·51 to 6·16)
Difference in risk of composite primary endpoint (RD% [95% CI])								
Versus placebo	−1·28 (−2·40 to −0·15)	−0·08 (−1·37 to 1·21)	−0·21 (−1·54 to 1·12)	..	1·59 (−0·42 to 3·59)	1·78 (−0·24 to 3·81)	0·37 (−1·53 to 2·26)	..
Versus nicotine patch	−1·07 (−2·21 to 0·08)	0·13 (−1·19 to 1·45)	..	..	1·22 (−0·81 to 3·25)	1·42 (−0·63 to 3·46)	..	..
Versus bupropion	−1·19 (−2·30 to −0·09)	..	..	..	−0·20 (−2·34 to 1·95)	..	..	..
Components of primary neuropsychiatric composite endpoint								
Anxiety‡	0	1 (0·1%)	0	3 (0·3%)	5 (0·5%)	4 (0·4%)	6 (0·6%)	2 (0·2%)
Depression‡	1 (0·1%)	0	0	0	6 (0·6%)	4 (0·4%)	7 (0·7%)	6 (0·6%)
Feeling abnormal‡	0	0	0	0	0	1 (0·1%)	0	0
Hostility‡	0	1 (0·1%)	1 (0·1%)	0	0	0	0	0
Agitation§	10 (1·0%)	11 (1·1%)	19 (1·9%)	11 (1·1%)	25 (2·4%)	29 (2·9%)	21 (2·1%)	22 (2·2%)
Aggression§	3 (0·3%)	3 (0·3%)	2 (0·2%)	3 (0·3%)	14 (1·4%)	9 (0·9%)	7 (0·7%)	8 (0·8%)
Delusions§	0	0	1 (0·1%)	0	1 (0·1%)	1 (0·1%)	1 (0·1%)	0
Hallucinations§	1 (0·1%)	0	0	0	5 (0·5%)	4 (0·4%)	2 (0·2%)	2 (0·2%)
Homicidal ideation§	0	0	1 (0·1%)	0	0	0	0	0
Mania§	0	1 (0·1%)	2 (0·2%)	2 (0·2%)	7 (0·7%)	9 (0·9%)	3 (0·3%)	6 (0·6%)
Panic§	0	4 (0·4%)	1 (0·1%)	3 (0·3%)	7 (0·7%)	16 (1·6%)	13 (1·3%)	7 (0·7%)
Paranoia§	0	1 (0·1%)	0	0	1 (0·1%)	0	0	2 (0·2%)
Psychosis§	0	0	1 (0·1%)	0	4 (0·4%)	2 (0·2%)	3 (0·3%)	1 (0·1%)
Suicidal behaviour§	0	1 (1·0%)	1 (0·1%)	0	1 (0·1%)	1 (0·1%)	0	1 (0·1%)
Suicidal ideation§	0	1 (0·1%)	2 (0·2%)	3 (0·3%)	5 (0·5%)	2 (0·2%)	3 (0·3%)†	2 (0·2%)
Completed suicide§	0	0	0	1 (0·1%)	0	0	0	0

(Table 2 continues on next page)

product kit codes did not allow deciphering of randomised treatment or block size. As such, participants, investigators, and research personnel were masked to treatment assignments.

Procedures

Participants set a target quit date 1 week after randomisation to coincide with the end of the titration for varenicline and bupropion and the initiation of nicotine patch treatment. Smoking cessation counselling of at most 10 min based on Agency for Healthcare Research and Quality guidelines[4] was given at each clinic visit. Participants were encouraged to complete all study visits even if treatment was discontinued.

At each study visit, pill and patch counts were done and documented to measure medication compliance. Compliance was defined as having any (partial or full) daily dose of study drug for 80% of the planned treatment period (ie, a minimum of 68 days). Using this metric, overall treatment compliance was about 80% across the four treatment conditions.

Tobacco and nicotine use were assessed with a structured questionnaire at all clinic visits and telephone contacts. All clinic visits included expired air carbon monoxide measurement. Emergence of adverse events was assessed with open-ended questions, direct observation, and a semi-structured Neuropsychiatric Adverse Events Interview (NAEI) done at all study visits by trained interviewers to fully capture neuropsychiatric adverse events of interest (appendix). The NAEI comprises 25 questions to probe for psychiatric symptoms during a clinical trial;[10] positive responses were considered possible neuropsychiatric adverse events that were assessed further by the trained interviewer by inquiring about each symptom's frequency, duration, and severity. General or psychiatric adverse events that met FDA requirements for serious adverse events—eg, resulting in death, admission to hospital, substantial disability, or life-threatening events—were classified accordingly. Additionally, investigators were instructed to assess whether positive responses on the C-SSRS,[20] and any proxy reports, such as from participants' family members or physicians, were neuropsychiatric adverse events.

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).[23,24] Aspects of psychiatric symptom severity were assessed at baseline and all visits with the C-SSRS,[20] and Hospital Anxiety and

	Non-psychiatric cohort* (n=3984)				Psychiatric cohort* (n=4074)			
	Varenicline (n=990)	Bupropion (n=989)	Nicotine patch (n=1006)	Placebo (n=999)	Varenicline (n=1026)	Bupropion (n=1017)	Nicotine patch (n=1016)	Placebo (n=1015)
(Continued from previous page)								
Primary composite neuropsychiatric endpoint (severe intensity only)	1 (0·1%)	4 (0·4%)	3 (0·3%)	5 (0·5%)	14 (1·4%)	14 (1·4%)	14 (1·4%)	13 (1·3%)
Components of primary neuropsychiatric composite endpoint (severe intensity only)								
Anxiety‡	0	1 (0·1%)	0	3 (0·3%)	5 (0·5%)	4 (0·4%)	6 (0·6%)	2 (0·2%)
Depression‡	1 (0·1%)	0	0	0	6 (0·6%)	4 (0·4%)	7 (0·7%)	6 (0·6%)
Feeling abnormal‡	0	0	0	0	0	1 (0·1%)	0	0
Hostility‡	0	1 (0·1%)	1 (0·1%)	0	0	0	0	0
Agitation‡	0	0	2 (0·2%)	0	1 (0·1%)	1 (0·1%)	4 (0·4%)	2 (0·2%)
Aggression‡	1 (1·0%)	1 (0·1%)	0	0	1 (0·1%)	1 (0·1%)	0	1 (0·1%)
Delusions‡	0	0	0	0	0	0	0	0
Hallucinations‡	0	0	0	0	0	1 (0·1%)	0	0
Homicidal ideation‡	0	0	0	0	0	0	0	0
Mania‡	0	0	0	0	2 (0·2%)	1 (0·1%)	0	0
Panic‡	0	1 (0·1%)	1 (0·1%)	1 (0·1%)	0	1 (0·1%)	0	1 (0·1%)
Paranoia‡	0	0	0	0	0	0	0	0
Psychosis‡	0	0	0	0	0	1 (0·1%)	1 (0·1%)	0
Suicidal behaviour‡	0	1 (0·1%)	0	0	1 (0·1%)	1 (0·1%)	0	1 (0·1%)
Suicidal ideation‡	0	0	0	1 (0·1%)	1 (0·1%)	0	1 (0·1%)	0
Completed suicide‡	0	0	0	1 (0·1%)	0	0	0	0
Events in the primary endpoint								
Serious adverse events¶	0	1 (0·1%)	2 (0·2%)	3 (0·3%)	6 (0·6%)	5 (0·5%)	3 (0·3%)†	3 (0·3%)
Resulting in permanent treatment discontinuations	1 (0·1%)	5 (0·5%)	7 (0·7%)	3 (0·3%)	16 (1·6%)	15 (1·5%)	12 (1·2%)	15 (1·5%)
Leading to interventions**	0	2 (0·2%)	1 (0·1%)	3 (0·3%)	7 (0·7%)	12 (1·2%)	7 (0·7%)	11 (1·1%)
Combined serious adverse events, severe adverse events, and leading to treatment discontinuations or interventions (at least one of)	2 (0·2%)	8 (0·8%)	8 (0·8%)	10 (1·0%)	28 (2·7%)	28 (2·8%)	21 (2·1%)†	29 (2·9%)

Data are n (%), unless otherwise stated. Based on least squares means analysis, point estimate, and its 95% CI. Estimated risk difference is based on a General Linear Model with terms treatment, cohort, region, and treatment by cohort interaction. Region uses two-level classification (USA, non-USA). Adverse events reported during treatment and 30 days or less after last dose. Participants are counted only once per each row, even if they have reported multiple events; participants can be counted in multiple rows. RD=risk difference. *All-treated population. †One additional participant in the nicotine patch group (psychiatric cohort) who reported moderate suicidal ideation (serious adverse events) was identified after the clinical database was locked; consequently, the participant was not included in the analysis of the primary study endpoint. ‡Severe intensity adverse events. §Moderate and severe intensity adverse event. ¶Serious adverse events were: non-psychiatric cohort: bupropion, suicide attempt (1); nicotine patch, suicide attempt (1), panic (1); placebo, suicidal ideation (2), completed suicide (1); psychiatric cohort: varenicline, suicidal ideation (2), depression (1), auditory hallucination (1), exacerbation of bipolar I disorder (1), anxiety plus self-injurious behaviour (1); bupropion, suicide attempt plus schizoaffective disorder (1), exacerbations of bipolar I disorder (2) and bipolar II disorder (1), emotional disorder plus neuropsychiatric symptoms (1); nicotine patch, anxiety (2), depression (1); placebo, suicide attempt (1), suicidal ideation (1), aggression (1). **Interventions include: psychotropic medication, psychotherapy, counselling, and admission to hospital.

Table 2: **Summary of primary neuropsychiatric composite safety endpoint and its components**

Depression Scale (HADS).[25] Participants who reported a severe neuropsychiatric adverse event, were considered to be at increased suicide risk, or had any substantial worsening of their psychiatric condition, underwent a psychiatric evaluation or risk assessment at that visit by a mental health professional who made specific treatment or intervention recommendations, including whether the participant could continue the study. The Fagerström Test for Cigarette Dependence (FTCD)[26] was used to assess cigarette dependence severity at baseline.

Outcomes

The primary endpoint was a composite measure based on post-marketing reports of neuropsychiatric adverse events in smokers taking varenicline and bupropion. It comprised 16 neuropsychiatric symptom categories that included 261 Medical Dictionary for Regulatory Activities version 18.0 (MedDRA, v.18.0)-derived preferred terms. The primary endpoint captured all volunteered, observed, and solicited neuropsychiatric adverse events (new events or increases in severity of ongoing symptoms) in these 16 components, irrespective of whether the site study physician assessed them to be causally related to study medications. The primary endpoint was met when participants reported at least one event coding to any of the 261 MedDRA-derived preferred terms across the 16 symptom categories during treatment or within 30 days of treatment discontinuation that met pre-established severity criteria. Adverse events were rated by trained investigators as mild (no interference with participant's

	Non-psychiatric cohort*(n=3984)				Psychiatric cohort* (n=4074)			
	Varenicline (n=990)	Bupropion (n=989)	Nicotine patch (n=1006)	Placebo (n=999)	Varenicline (n=1026)	Bupropion (n=1017)	Nicotine patch (n=1016)	Placebo (n=1015)
During treatment and ≤30 days after last dose								
Assessed	988	983	996	995	1017	1012	1006	1006
Suicidal behaviour and/or ideation	7 (1%)	4 (<1%)	3 (<1%)	7 (1%)	27 (3%)	15 (1%)	20 (2%)	25 (2%)
Suicidal behaviour†‡	0	0	1 (<1%)	1 (<1%)§	0	1 (<1%)	0	2 (<1%)
Suicidal ideation	7 (1%)	4 (<1%)	3 (<1%)	6 (1%)	27 (3%)	15 (1%)	20 (2%)	25 (2%)
During follow-up (>30 days after last treatment dose and through end of study)								
Assessed	807	816	800	805	833	836	824	791
Suicidal behaviour and/or ideation	3 (<1%)	2 (<1%)	3 (<1%)	4 (<1%)	14 (2%)	4 (<1%)	9 (1%)	11 (1%)
Suicidal behaviour†¶	0	1 (<1%)	0	0	1 (<1%)	0	1 (<1%)	1 (<1%)
Suicidal ideation	3 (<1%)	2 (<1%)	3 (<1%)	4 (<1%)	14 (2%)	4 (<1%)	9 (1%)	11 (1%)

Data are n or n (%). *All-treated population. †Suicidal behaviour (most severe for each participant with positive answers on the C-SSRS). ‡During treatment: non-psychiatric cohort: nicotine patch, suicide attempt (1); placebo, completed suicide (1); psychiatric cohort: bupropion, suicide attempt (1); placebo, suicide attempt (2). §Completed suicide. ¶During follow-up: non-psychiatric cohort: bupropion, suicide attempt (1); psychiatric cohort: varenicline, suicide attempt (1); nicotine patch, aborted attempt (1); placebo, aborted attempt (1).

Table 3: **Columbia-Suicide Severity Rating Scale (C-SSRS)**

usual daily functioning), moderate (some interference with functioning), or severe (substantial interference). Prespecified severity criteria for the primary neuropsychiatric adverse event endpoint required adverse events for the four components expected to be reported more commonly (anxiety, depression, feeling abnormal, or hostility) to be rated as severe. Neuropsychiatric adverse events in the remaining 12 categories (agitation, aggression, delusions, hallucinations, homicidal ideation, mania, panic, paranoia, psychosis, suicidal ideation, behaviour, or completed suicide) met severity criteria when rated as either moderate or severe. A simplified scheme of the primary composite safety endpoint is shown in the appendix.

Secondary safety endpoints included the subset of all neuropsychiatric adverse events that were rated severe and the occurrence of each of the individual components. Other safety assessments included psychiatric rating scales (see below), all adverse events, vital signs, and select laboratory values. Cardiovascular safety data will be reported separately, after completion of the 28-week non-treatment extension phase.

The primary efficacy endpoint for smoking cessation was the continuous abstinence rate for weeks 9–12. Participants were considered abstinent who self-reported tobacco abstinence throughout the period in conjunction with no exhaled carbon monoxide concentration greater than 10 ppm. Missing self-reports before week 12 were imputed via a backward carry method (missing at week 12 was deemed a smoker). Missing carbon monoxide measurements were imputed as less than 10 ppm, but a sensitivity analysis was also done imputing missing values as smoking. In accordance with recommended practice,[27] participants who were lost to follow-up were considered to be smokers. The pre-designated secondary efficacy endpoint was carbon monoxide-confirmed continuous abstinence for weeks 9–24 defined similarly. 7-day-point-prevalence of abstinence at all visits or contacts was also a prespecified outcome.

Statistical analysis

The sample for this study was driven by a requirement to estimate the size of increase in the rate of neuropsychiatric adverse events relative to the placebo group with a prespecified level of precision. Based on pooled data from previous randomised controlled trials,[28] the underlying placebo rates for neuropsychiatric adverse events in the non-psychiatric cohort and psychiatric cohort were postulated to be 3·5% and 7·0%, respectively. A sample size of 2000 per treatment group was determined to be sufficient to estimate a 75% increase in neuropsychiatric adverse event rate within +1·59% or –1·59%. The sample size is also sufficient to detect a two-fold increase in the odds of abstinence rate in the placebo group.

Point and interval estimates of risk differences (RDs; ie, differences in percentages of incidence of neuropsychiatric adverse events), were obtained using generalised linear regression with terms to account for treatment, cohort (non-psychiatric cohort and psychiatric cohort), region (reduced to two regions: USA and non-USA), and interactions. Differences were considered significant if their associated 95% CIs were entirely below or above zero. Logistic regression analysis was used for the analysis of abstinence endpoints. The estimates of odds ratios (ORs) and corresponding 95% CIs were obtained via linear contrasts.

All participants randomised to study medications comprised the population for efficacy analyses and participants treated with study medications comprised the population for analysis of safety. The varenicline and bupropion comparisons versus placebo were prespecified as primary; all other treatment comparisons were deemed

	Non-psychiatric cohort† (n=3984)				Psychiatric cohort† (n=4074)			
	Varenicline (n=990)	Bupropion (n=989)	Nicotine patch (n=1006)	Placebo (n=999)	Varenicline (n=1026)	Bupropion (n=1017)	Nicotine patch (n=1016)	Placebo (n=1015)
Psychiatric disorders	315 (32%)	332 (34%)	301 (30%)	259 (26%)	405 (39%)	435 (43%)	420 (41%)	354 (35%)
Abnormal dreams	83 (8%)	47 (5%)	111 (11%)	39 (4%)	118 (12%)	84 (8%)	140 (14%)	53 (5%)
Agitation	32 (3%)	29 (3%)	28 (3%)	25 (3%)	47 (5%)	56 (6%)	39 (4%)	41 (4%)
Anger	3 (<1%)	1 (<1%)	1 (<1%)	3 (<1%)	11 (1%)	4 (<1%)	4 (<1%)	5 (<1%)
Anxiety‡	46 (5%)	64 (6%)	45 (4%)	57 (6%)	86 (8%)	105 (10%)	93 (9%)	63 (6%)
Depressed mood	31 (3%)	13 (1%)	27 (3%)	29 (3%)	47 (5%)	47 (5%)	52 (5%)	52 (5%)
Depression	17 (2%)	13 (1%)	8 (1%)	15 (2%)	49 (5%)	45 (4%)	47 (5%)	46 (5%)
Depressive symptom	5 (1%)	3 (<1%)	2 (<1%)	2 (<1%)	11 (1%)	8 (1%)	12 (1%)	13 (1%)
Initial insomnia	7 (1%)	6 (1%)	10 (1%)	4 (<1%)	15 (1%)	8 (1%)	10 (1%)	2 (<1%)
Insomnia	95 (10%)	126 (13%)	91 (9%)	73 (7%)	94 (9%)	119 (12%)	104 (10%)	66 (7%)
Irritability	34 (3%)	29 (3%)	47 (5%)	37 (4%)	48 (5%)	42 (4%)	61 (6%)	67 (7%)
Major depression	3 (<1%)	0	1 (<1%)	3 (<1%)	7 (1%)	10 (1%)	4 (<1%)	2 (<1%)
Middle insomnia	7 (1%)	15 (2%)	13 (1%)	6 (1%)	11 (1%)	16 (2%)	13 (1%)	8 (1%)
Nervousness	14 (1%)	18 (2%)	11 (1%)	9 (1%)	21 (2%)	19 (2%)	17 (2%)	27 (3%)
Nightmare	9 (1%)	7 (1%)	26 (3%)	3 (<1%)	13 (1%)	9 (1%)	30 (3%)	14 (1%)
Panic attack	2 (<1%)	7 (1%)	2 (<1%)	3 (<1%)	9 (1%)	19 (2%)	13 (1%)	11 (1%)
Restlessness	14 (1%)	14 (1%)	15 (1%)	14 (1%)	17 (2%)	20 (2%)	14 (1%)	9 (1%)
Sleep disorder	31 (3%)	37 (4%)	17 (2%)	19 (2%)	34 (3%)	36 (4%)	28 (3%)	23 (2%)
Tension	2 (<1%)	10 (1%)	2 (<1%)	2 (<1%)	9 (1%)	5 (<1%)	10 (1%)	6 (1%)

Data are n (%).*As classified by the Medical Dictionary for Regulatory Activities (MedDRA, version 18.0) in the System Organ Class category of psychiatric disorders and derived preferred terms, and occurring during treatment and at most 30 days after last dose. †All-treated population. ‡As per MedDRA (version 18.0) preferred term Anxiety; this differs from the Anxiety component of the primary composite endpoint, which is a cluster of several MedDRA (version 18.0) preferred terms related to anxiety disorders; the same note applies to other preferred terms in this table (eg, depression, agitation).

Table 4: **Mild, moderate, or severe adverse events* coding to the MedDRA category psychiatric disorders reported by at least 1% of participants in any treatment group**

secondary. No adjustments for multiplicity of testing were made. The trial is registered at ClinicalTrials.gov (number NCT01456936) and is now closed.

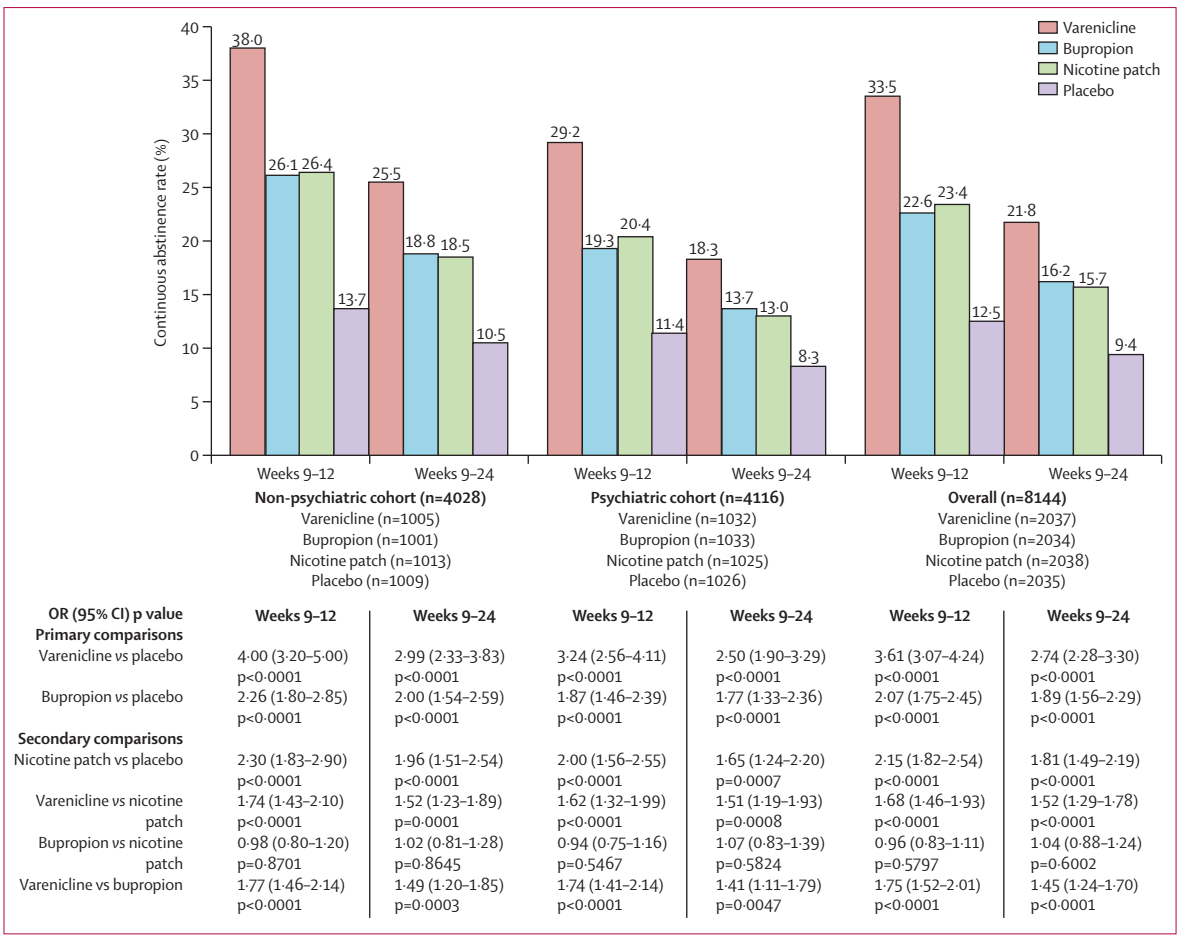
Role of the funding source

The study is a post-marketing requirement in the USA for Pfizer and GlaxoSmithKline. As such, the study was designed by sponsor employees (with input from AK, LSA, DL, and CR) and academic authors (RMA, and also with input from NLB, AEE, and RW). The lead academic (corresponding) author prepared the initial draft of the manuscript. All authors were involved with the acquisition, analysis, or interpretation of the data and critically revised the manuscript for important intellectual content. The lead academic author had full access to all data in the study and had final responsibility for the decision to submit for publication. All authors assume responsibility for the completeness and integrity of the data and for the fidelity of the study to the protocol and statistical analysis plan.

Results

Between Nov 30, 2011, and Jan 13, 2015, 11 186 smokers were screened, of which 8144 (73%) were randomly assigned to a non-psychiatric cohort (n=4028) and a psychiatric cohort (n=4116; figures 1 and 2). Among treated participants in the non-psychiatric cohort (n=3984) and psychiatric cohort (n=4074), 3145 (79%) and 3023 (74%), respectively, completed treatment, and 3124 (78%) and 3169 (78%) participants, respectively, completed the study (figures 1 and 2). Reasons for discontinuations were similar across cohorts and treatment groups.

Baseline demographic, smoking, and psychiatric characteristics for all treated participants are presented in table 1. Overall the study population included 3549 (44%) men, had an average age of 46·5 years, and 6584 (82%) participants of white race and ethnicity. Most participants came from the USA (4207 [52%]). Participants smoked an average of 21 cigarettes per day with an average FTCD of 5·8 and 6647 (82%) participants had made at least one previous attempt to quit. The treatment groups had similar baseline characteristics within cohorts, but smokers in the psychiatric cohort were more likely to be female, reside in the USA, and have higher FTCD scores (table 1). Smokers in the psychiatric cohort met DSM-IV-TR criteria for primary mood (2882 [71%] participants), anxiety (782 [19%] participants), psychotic (386 [9%] participants), and borderline personality disorders (24 [<1%] participants), and 1996 (49%) participants were taking psychotropic medications at baseline. In the psychiatric cohort,



OR (95% CI) p value	Weeks 9–12	Weeks 9–24	Weeks 9–12	Weeks 9–24	Weeks 9–12	Weeks 9–24
Primary comparisons						
Varenicline *vs* placebo	4·00 (3·20–5·00) p<0·0001	2·99 (2·33–3·83) p<0·0001	3·24 (2·56–4·11) p<0·0001	2·50 (1·90–3·29) p<0·0001	3·61 (3·07–4·24) p<0·0001	2·74 (2·28–3·30) p<0·0001
Bupropion *vs* placebo	2·26 (1·80–2·85) p<0·0001	2·00 (1·54–2·59) p<0·0001	1·87 (1·46–2·39) p<0·0001	1·77 (1·33–2·36) p<0·0001	2·07 (1·75–2·45) p<0·0001	1·89 (1·56–2·29) p<0·0001
Secondary comparisons						
Nicotine patch *vs* placebo	2·30 (1·83–2·90) p<0·0001	1·96 (1·51–2·54) p<0·0001	2·00 (1·56–2·55) p<0·0001	1·65 (1·24–2·20) p=0·0007	2·15 (1·82–2·54) p<0·0001	1·81 (1·49–2·19) p<0·0001
Varenicline *vs* nicotine patch	1·74 (1·43–2·10) p<0·0001	1·52 (1·23–1·89) p=0·0001	1·62 (1·32–1·99) p<0·0001	1·51 (1·19–1·93) p=0·0008	1·68 (1·46–1·93) p<0·0001	1·52 (1·29–1·78) p<0·0001
Bupropion *vs* nicotine patch	0·98 (0·80–1·20) p=0·8701	1·02 (0·81–1·28) p=0·8645	0·94 (0·75–1·16) p=0·5467	1·07 (0·83–1·39) p=0·5824	0·96 (0·83–1·11) p=0·5797	1·04 (0·88–1·24) p=0·6002
Varenicline vs bupropion	1·77 (1·46–2·14) p<0·0001	1·49 (1·20–1·85) p=0·0003	1·74 (1·41–2·14) p<0·0001	1·41 (1·11–1·79) p=0·0047	1·75 (1·52–2·01) p<0·0001	1·45 (1·24–1·70) p<0·0001

Figure 3: **Continuous abstinence rates for weeks 9–12 and 9–24**
Analyses based on the all-randomised population. OR=odds ratio.

1377 (34%) participants had a history of suicidal ideation and 514 (13%) participants had a history of suicidal behaviour based on the C-SSRS.

The overall incidence of the neuropsychiatric adverse event endpoint was similar across the four treatment groups: varenicline 4·0% (80 of 2016 participants), bupropion 4·5% (90 of 2006 participants), nicotine patch 3·9% (78 of 2022 participants), and placebo 3·7% (74 of 2014 participants). There were more neuropsychiatric adverse events in the psychiatric cohort (5·8%, 238 of 4074 participants) than the non-psychiatric cohort (2·1%, 84 of 3984 participants; p<0·0001 for the cohort effect; table 2). There was a treatment by cohort interaction (p=0·0652), so analyses of neuropsychiatric adverse events by treatment assignment are presented for each cohort separately. For the non-psychiatric cohort, the risk for the composite safety endpoint was lower for participants assigned to varenicline than those assigned to placebo (RD –1·28, 95% CI –2·40 to –0·15), although there was no significant difference in neuropsychiatric adverse events in those assigned to bupropion versus placebo (RD –0·08, –1·37 to 1·21). Differences between varenicline and nicotine patch and between bupropion and nicotine patch were also not significant in the non-psychiatric cohort. In the psychiatric cohort, there were no significant pairwise treatment differences (95% CIs included zero).

A third or fewer of the participants (between two and five per treatment group in the non-psychiatric cohort and ten and 17 in the psychiatric cohort) who met the primary safety endpoint reported more than one neuropsychiatric adverse event (appendix). Of the participants reporting the primary neuropsychiatric endpoint, the percentage of those reporting neuropsychiatric adverse events that were severe, met serious adverse event criteria, or led to treatment discontinuations or interventions (ie, the clinically most significant events), was lower in the non-psychiatric cohort than the psychiatric cohort and was similar across treatment groups (table 2).

The number of participants reporting suicidal ideation or behaviour on the C-SSRS was greater in the psychiatric cohort than in the non-psychiatric cohort and similar across treatment groups (table 3). There was one

completed suicide in the study in a placebo-treated participant in the non-psychiatric cohort. The average total HADS score improved from baseline through the treatment phase by about 2 points in the non-psychiatric cohort and 3 points in the psychiatric cohort, an effect that was similar across the treatment groups (appendix).

Table 4 lists all adverse events (mild, moderate, and severe) in the Psychiatric Disorder MedDRA category occurring in at least 1% of any treatment group in either cohort, irrespective of whether they met the criteria for the primary neuropsychiatric adverse event endpoint. Those in the psychiatric cohort were more likely to report neuropsychiatric adverse events of all types than those in the non-psychiatric cohort. The profile of adverse events exhibited (eg, abnormal dreams more common for varenicline and nicotine patch compared with placebo) was consistent with previous reports. Incidences of general adverse events, serious adverse events, deaths, treatment discontinuations, and adverse events observed in at least 5% of participants are summarised in the appendix. Overall, the treatments were well tolerated. In brief, across cohorts, the most frequent adverse events by treatment group were nausea (varenicline, 25% [511 of 2016 participants]), insomnia (bupropion, 12% [245 of 2006 participants]), abnormal dreams (nicotine patch, 12% [251 of 2022 participants]), and headache (placebo, 10% [199 of 2014 participants]).

As specified in the study protocol, an analysis was undertaken to assess whether treatment efficacy varied between the non-psychiatric cohort and psychiatric cohort, and although the abstinence rates are lower in the psychiatric cohort versus non-psychiatric cohort (figure 3), no evidence was found for an interaction (p=0·6237). The continuous abstinence rates for weeks 9–12 and 9–24 by treatment and the ORs for all pairwise comparisons are presented for the combined sample as well as for the two cohorts in figure 3. Varenicline showed superior efficacy to placebo and to both nicotine patch and bupropion at end of treatment (weeks 9–12) and follow-up (weeks 9–24). Bupropion showed similar efficacy to nicotine patch and both showed superior efficacy versus placebo. Imputing missing carbon monoxide measurements that occurred in 72 participants self-reporting continuous abstinence during weeks 9–24 as smoking did not significantly affect the results (appendix). 7-day point prevalence of abstinence for weeks 1–24 show results consistent with the continuous abstinence rates (appendix).

Discussion

Our large multinational trial did not show a significant increase in rates of moderate-to-severe neuropsychiatric adverse events with either varenicline or bupropion relative to nicotine patch or placebo in those with or without psychiatric disorders. We did not find treatment-associated changes on validated, longitudinal assessments of suicidality using the C-SSRS, of mood and anxiety symptoms with the HADS, or conventional assessments of neuropsychiatric adverse events including treatment discontinuation. Varenicline showed superior efficacy to bupropion and nicotine patch in both cohorts, whereas bupropion had similar efficacy to nicotine patch with both showing superior efficacy to placebo in both cohorts.

Interpreting the CIs for the primary outcome measure, our findings make it highly unlikely that varenicline or bupropion increase moderate-to-severe neuropsychiatric adverse events by more than 1·5 percentage points in smokers without psychiatric disorders, and by 4 percentage points in smokers with psychiatric disorders based on the upper bounds of the 95% CIs. They are also consistent with there being no increase in neuropsychiatric adverse events in either population of smokers.

The study detected about a 4 percentage point significant difference in the rate of neuropsychiatric adverse events between the psychiatric and non-psychiatric cohorts. Moreover, the observed incidence was close to the postulated values—about 2% in the non-psychiatric cohort and 6% in the psychiatric cohort—so it seems unlikely that failure to detect medication effects was attributable to lack of sensitivity of the measures or selection of smokers with unusually good mental health.

These results add substantially to those of the previous meta-analyses of randomised controlled trials[12–14] and observational studies,[9,15,16,29] using a rigorous experimental design and very detailed proactive assessment of treatment-emergent and post-treatment neuropsychiatric symptoms, thereby addressing limitations of the previous studies. Therefore, they provide important new information on which regulators, prescribers, and smokers can make an informed choice when deciding how best to address nicotine dependence.

Our findings show for the first time that the efficacy of the medications in terms of ORs is similar for smokers with or without psychiatric disorders. Smokers in the psychiatric cohort achieved lower abstinence rates than those in the non-psychiatric cohort, so the absolute effect size was smaller in those with psychiatric disorders than those without, but it was still substantial. Moreover, inspection of the 7-day point prevalence of abstinence curves reveals a similar recruitment to abstinence effect previously described in non-psychiatrically ill smokers with varenicline. Further analyses will be helpful in assessing whether there is any evidence of differential effectiveness as a function of the severity of the psychiatric disorder or diagnostic category.

This study provides the first evidence of comparative efficacy between the three main pharmacological treatments to aid smoking cessation in a double-blind and triple-dummy trial. The size of the differences is similar to what was predicted from the Cochrane network meta-analysis.[1] The fact that this study was done in many centres in countries with widely different attitudes regarding tobacco use, confirms the generalisability of these conclusions across cultures.

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Our results appear to differ from a recent open-label study that compared varenicline with combination nicotine replacement therapy (nicotine patch plus lozenge) and single formulation nicotine replacement therapy (nicotine patch).[17] On the most comparable outcome measure of prolonged abstinence at 26 weeks, that study found an OR of 1·1, but with a relatively small sample size, the 95% CI (0·7 to 1·7) overlapped with the point estimate found in the present study (1·52) and with the estimate from the Cochrane network meta-analysis (1·57).

The present study has several limitations. First, we included smokers with psychiatric disorders who were stable and treated or who had previous psychiatric conditions (eg, major depressive disorder) that were in remission. Thus, these selection effects might have affected the findings, and our results might not generalise to those with untreated or symptomatically unstable psychiatric illness. Similarly, we restricted the scope of the psychiatric cohort to smokers in four major disease categories—mood, anxiety, psychotic, and borderline personality disorders—and excluded participants with other current substance use disorders or who were at imminent risk for suicide, further limiting generalisability. Second, the 24-week duration of the study and frequent monitoring might not mirror a real-world smoking cessation attempt. Third, although this is the largest double-blind, placebo-controlled safety and efficacy trial of pharmacotherapy for smoking cessation done to date, some of the sub-cohorts in the psychiatric cohort are smaller than others, our study was not powered to detect differences in rare events such as completed suicides, nor can we rule out, based on the upper bound 95% CIs, an increase of serious neuropsychiatric adverse events as defined of up to 4% in the psychiatric cohort. Fourth, we recruited individuals who smoked, on average, at least ten cigarettes per day and who were moderately nicotine dependent. Thus, our findings might not generalise to lighter, less severely dependent smokers. Fifth, our analyses did not consider the potential moderating effects of sex, dependence severity, and depression or anxiety symptoms between the cohorts, which were not pre-specified in our statistical analysis plan, but will be considered along with other predictor variables in subsequent publications. Finally, attrition occurred across all treatment groups between both cohorts, and missing data could have affected outcomes. These limitations aside, the lack of any signal for serious neuropsychiatric adverse events in this and other randomly controlled trials,[10–14,30] combined with the growing number of studies finding no such association in large cohorts of smokers with or without psychiatric disorders,[9,15,16,29] makes it improbable that use of these medications in psychiatrically stable smokers is causally associated with a heightened neuropsychiatric safety risk.

In summary, in the context of evidence from clinical trials and observational cohort studies, this large, multinational trial provides further evidence that varenicline and bupropion can be used safely by psychiatrically stable smokers. Although varenicline appears to be the most effective single pharmacotherapy available, all of the first-line medications—varenicline, bupropion, and nicotine patch—are efficacious compared with placebo.

Contributors

RMA and DL had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. RMA, LSA, NLB, AEE, AK, DL, CR, and RW had input to study design. DL and AK did the statistical analyses. LSA, DL, and TM were involved in study supervision. All authors were involved in acquisition, analysis, or interpretation of data. RMA drafted the manuscript and all authors were involved in the critical revision of the manuscript for important intellectual content.

Declaration of interests

RMA reports receiving grants from Pfizer and Alkermes, and providing consulting and advisory board services to Pfizer, Arena Pharmaceuticals, and Cerecor. RMA's writing of this manuscript was supported, in part, by National Institute on Alcohol Abuse and Alcoholism grant numbers U01 AA013641 and R01 AA019720; National Institute on Drug Abuse/Veterans Affairs Cooperative Studies numbers 1031 and 1032; and Veterans Affairs Merit Award number NEUA-003-08S. NLB reports providing consulting and advisory board services to Pfizer and GlaxoSmithKline, and having been a paid expert witness in litigation against tobacco companies. RW reports receiving grants from Pfizer, Johnson & Johnson, and GlaxoSmithKline, and receiving personal fees for advisory board services from Pfizer and GlaxoSmithKline. RW's salary is funded by Cancer Research UK. AEE reports receiving grants from Pfizer and Forum Pharmaceuticals, and receiving personal fees for advisory board services from Pfizer and Reckitt Benckiser. AEE's writing of the manuscript was supported by a National Institute on Drug Abuse Career Award in Patient-Oriented Research, number K24 DA030443. LSA, TM, DL, and CR are employees and stockholders of Pfizer. JA is an employee of GlaxoSmithKline and stockholder of that company. AK is a PAREXEL employee working on behalf of GlaxoSmithKline. The opinions expressed in this Article are the authors' own, and do not necessarily reflect the views of their employers.

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