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Original Investigation

Psychiatric Comorbidity and Multimorbidity in the EAGLES Trial: Descriptive Correlates and Associations With Neuropsychiatric Adverse Events, Treatment Adherence, and Smoking Cessation

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Abstract

Introduction: Psychiatric and substance use disorders represent barriers to smoking cessation. We sought to identify correlates of psychiatric comorbidity (CM; 2 diagnoses) and multimorbidity (MM; 3+ diagnoses) among smokers attempting to quit and to evaluate whether these conditions predicted neuropsychiatric adverse events (NPSAEs), treatment adherence, or cessation efficacy (CE).

Aims and Methods: Data were collected from November 2011 to January 2015 across sixteen countries and reflect the psychiatric cohort of the EAGLES trial. Participants were randomly assigned to receive varenicline, bupropion, nicotine replacement therapy, or placebo for 12 weeks and were followed for an additional 12 weeks posttreatment. NPSAE outcomes reflected 16 moderate-to-severe neuropsychiatric symptom categories, and CE outcomes included continuous abstinence at weeks 9–12 and 9–24.

Results: Of the 4103 participants included, 36.2% were diagnosed with multiple psychiatric conditions (20.9% CM, 15.3% MM). Psychiatric CM and MM were associated with several baseline factors, including male gender, nonwhite race or ethnicity, more previous quit attempts, and more severe mental health symptoms. The incidence of moderate-to-severe NPSAEs was significantly higher ($p < .01$) in participants with MM (11.9%) than those with CM (5.1%) or primary diagnosis only (4.6%). There were no significant ($ps > .05$) main effects or interactions with treatment condition for diagnostic grouping on treatment adherence or CE outcomes.

Conclusions: While having multiple psychiatric diagnoses increased risk of developing moderate-to-severe NPSAEs during a quit attempt, neither CM nor MM were associated with treatment adherence or odds of quitting. These findings reassure providers to advise smokers with multiple stable psychiatric conditions to consider using Food and Drug Administration (FDA)-approved medications when trying to quit.

Implications: Psychiatric MM may be associated with development of NPSAEs when smokers make a medication-assisted quit attempt, but it does not appear to be differentially associated with medication compliance or efficacy. Prescribing healthcare professionals are encouraged to not only promote use of FDA-approved pharmacotherapies by smokers with complex psychiatric presentations, but also to closely monitor such smokers for neuropsychiatric side effects that may be related to their mental health conditions.
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Introduction

While prevalence of cigarette smoking in the general population is declining both globally[1] and within the United States (US),[2] smoking remains a major public health concern, especially within populations that are disparately affected by tobacco-related morbidity and mortality. One such at-risk population is individuals diagnosed with mental health conditions, which can include both psychiatric (PD) and substance use disorders (SUD). Epidemiological data from the US consistently indicate that, when compared with individuals without such diagnoses, this population smokes at higher rates[3,4] and has more difficulty quitting.[5,6] In fact, data from the 2018 National Survey on Drug Use and Health indicate that prevalence of smoking among individuals with a mental health condition is 72% higher than individuals without such a condition.[7] Additional epidemiological data suggest that tobacco-related mortality is elevated among individuals receiving substance use or dual diagnosis treatment services,[8] and within individuals with significant psychological distress, smoking can result in a shortened life expectancy of nearly 10 years.[9] These findings from the US have been reported alongside guidelines from international agencies like the World Health Organization,[10] the Royal College of Physicians and Royal College of Psychiatrists[11] and the Australian Government Department of Health[12] that offer valuable perspectives, recommendations, and resources on how to promote successful cessation among smokers with PD and SUD. Taken together, population-based data and guidance from international health organizations converge to support the long-held perspective that mental health conditions, including PD and SUD, represent persistent tobacco-related health disparities that could potentially limit the impact and efficacy of smoking cessation treatments.[13,14]

Despite these well-established relationships, several cultural and systemic barriers make accessing and implementing smoking cessation treatments challenging for smokers with mental health conditions. These barriers include myths about the utility of smoking for managing psychiatric symptoms and risks of quitting smoking on exacerbation of such symptoms,[15] as well as limited provider training in tobacco use treatment and limited time available to deliver said treatments.[16] Therefore, researchers have committed extensive resources to addressing these disparities and to evaluating how different categories of PD and SUD might impact smoking cessation. Randomized controlled trials have demonstrated that treatments can effectively promote cessation among smokers with co-occurring depression,[17] posttraumatic stress disorder,[18] alcohol dependence,[19] opioid dependence,[20] and schizophrenia,[21] among other diagnoses. Meta-analyses also indicate that smoking cessation pharmacotherapies are effective at smoking cessation and reduction for smokers with severe mental illness.[22,23] These data reinforce the idea that smoking cessation aided by evidence-based methods is achievable in this at-risk population despite the complexity that comes with managing smokers with mental health conditions.

Although these results are promising, there has been significantly less research into the impact of mental health multimorbidity (MM) on smoking cessation. MM has been traditionally used to describe co-occurring chronic medical conditions and is typically differentiated from comorbidity (CM) based on the number of conditions that are co-occurring with the primary clinical condition. While CM accounts for one distinct clinical condition co-occurring with a primary clinical condition, MM represents the co-occurrence of multiple clinical conditions alongside the primary clinical condition being studied.[24] The presence of multiple co-occurring conditions can make it challenging for clinicians to identify primary or secondary treatment targets, especially when co-occurring conditions possess common biopsychosocial factors. As interest in MM has expanded in recent years, PD and SUD have been identified as critical aspects of the conceptualization of this construct.[25]

MM research has been described as "in its infancy,"[26] and the Academy of Medical Sciences[27] recently identified reporting trends and patterns of MM and evaluating benefits and risks of treatment among patients as high-priority research areas. Further, the Global Alliance for Chronic Disease, a multidisciplinary international network of healthcare professionals, researchers, and stakeholders, recently released a statement reinforcing the limited nature of MM research and evidence-based healthcare guidelines for individuals with MM.[28] Organizational statements such as these make it clear that MM treatment research (including projects related to mental health conditions) are critical and have the potential to make valuable contributions to advancing healthcare services.

One study that enables exploration of these important questions as they relate to smoking cessation is the Evaluating Adverse Events in a Global Smoking Cessation Study (EAGLES).[29] EAGLES was designed to evaluate the neuropsychiatric safety and efficacy of smoking cessation medications within smokers diagnosed with primary PD, and recently published data suggest that varenicline, bupropion, and nicotine replacement therapy (NRT) were well tolerated by smokers diagnosed with primary mood, anxiety, and psychotic disorders.[30–32] The inclusion criteria for EAGLES allowed for smokers with comorbid PD and with past histories of SUD to participate, so long as they met diagnostic criteria for a primary mood, anxiety, or psychotic disorder. This makes data from the EAGLES trial uniquely suited to extend these findings and identify correlates and outcomes associated with mental health CM and MM. Thus, the specific aims of this post hoc secondary analysis of data from the EAGLES trial were to: (1) describe baseline prevalence, correlates, and patterns of mental health CM and MM within the psychiatric cohort of the EAGLES trial; (2) determine whether mental health CM or MM was a risk factor for developing moderate-to-severe neuropsychiatric

adverse events (NPSAEs) while participating in the EAGLES trial; and (3) evaluate the extent to which mental health CM and MM was associated with adherence to and efficacy of smoking cessation medications in the EAGLES trial.

Methods

Design

As described in detail elsewhere,[29] EAGLES was a multinational, multisite, double-blind, triple-dummy, placebo-controlled trial that randomized smokers to receive varenicline (1 mg twice daily), bupropion (150 mg twice daily), NRT (21 mg patch with taper), or placebo for a period of 12 weeks (ClinicalTrials.gov Identifier NCT01456936). EAGLES was a safety and efficacy trial designed to comply with postmarketing requirements from the U.S. Food and Drug Administration (FDA) and to serve as a postauthorization safety study for the European Medicines Agency. All participants received brief smoking cessation counseling throughout the treatment period and were followed for an additional 12 weeks, yielding 24 total weeks of study participation. Data collection was conducted from November 2011 through January 2015.

Participants

Participants included in this secondary analysis were individuals who composed the psychiatric cohort of the EAGLES trial who were randomized to one of the four treatment conditions (n = 4103). These participants had been diagnosed with primary mood disorders (major depression, bipolar I, bipolar II), anxiety disorders (panic disorder with or without agoraphobia, posttraumatic stress disorder, obsessive compulsive disorder, social phobia, generalized anxiety disorder), psychotic disorders (schizophrenia or schizoaffective), or borderline personality disorder. Diagnoses were made at baseline via the research version of the Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID-I)[33] and the Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II).[34] All SCID-I and SCID-II interviews were conducted by trained Masters-level or above research assessors, and final diagnoses were confirmed by a doctoral level (MD or PhD) provider. SCID interviews were monitored for fidelity and integrity by independent vendors, and all assessors received clinical supervision from doctoral level providers. Diagnoses were not independently confirmed via review of existing external medical records.

EAGLES enrolled smokers with comorbid and multimorbid PD and SUD, including co-occurring alcohol or substance abuse and dependence as diagnosed by the SCID-I. Any SUD reflected a lifetime diagnosis and had to have been in sustained full remission for at least 12 months upon enrolling in the trial, and participants could not be actively taking opioid agonists or partial agonists to participate. Participants were not assessed for a DSM-IV-TR diagnosis of Nicotine Use Disorder, as this was not included in the version of the SCID-I interview that was administered at baseline. Participants were also required to have reported clinically stable psychiatric symptomology for a period of 6 months upon recruitment into the trial. If they endorsed receiving psychiatric treatment for their disorder at screening, they were required to have been stable on their medication type and dose for a period of at least 3 months. Finally, participants could not be at high risk for suicide, which was defined by self-reporting no suicidal ideation with intent or plan and no suicidal behavior in the past year at baseline.

Baseline Measures

Demographic, mental health, smoking-related, and medication-related baseline variables were all considered to develop profiles of psychiatric CM and MM. Demographic factors included age, gender (male or female), race (white or nonwhite), body weight, body mass index, number of lifetime medical comorbidities, and region of enrollment (US or non-US). Mental health assessments done at baseline included the Clinical Global Impression—Severity subscale (CGI-S),[35] the depression and anxiety symptom subscales of the Hospital Anxiety and Depression Scale (HADS),[36] the Buss–Perry Aggression Questionnaire (BPAQ),[37] and the Columbia Suicide Severity Rating Scale (C-SSRS).[38] Baseline smoking-related characteristics included number of years spent smoking, current number of cigarettes per day, number of previous quit attempts, and cigarette dependence measured via the Fagerström Test for Cigarette Dependence (FTCD).[39] Finally, medication histories assessed at baseline included current use of any psychiatric medications, current use of specific psychiatric medications (ie, antidepressants, anxiolytics, antipsychotics, mood stabilizers), and prior use of smoking cessation pharmacotherapies (ie, varenicline, bupropion, and NRT). These histories were primarily collected via participant self-report, and research staff were given permission by participants upon enrollment to ask them to provide pill bottles or to provide staff with contact information for mental health providers.

Neuropsychiatric Outcomes

The primary neuropsychiatric safety outcome in the EAGLES trial was a composite measure of NPSAEs that has been described previously.[29] Briefly, the composite measure was composed of 16 neuropsychiatric symptom categories mapped across 261 preferred terms found in the Medical Dictionary for Regulatory Activities, version 18.0 (MedDRA, v.18.0). In addition to recording any volunteered or observed NPSAEs, specific psychiatric symptoms were solicited with an interview that had been administered in previous evaluations of the efficacy of varenicline among smokers with mental health comorbidities.[40] The primary safety endpoint was met when at least one symptom was captured at a prespecified level of severity during treatment or within 30 days of treatment discontinuation. The 16 symptom categories included 4 that required a rating as severe to qualify in the composite endpoint (abnormal feelings, anxiety, depression, hostility) and 12 that required rating of at least moderate to qualify (aggression, agitation, delusion, hallucination, mania, panic, paranoia, psychosis, homicidal ideation, suicidal ideation, suicidal behaviors, and suicide completion).

Treatment Compliance and Smoking Cessation Outcomes

One treatment adherence and two smoking cessation efficacy outcomes were also considered for the analyses. Treatment adherence was prespecified as a categorical variable that identified "compliant" participants, which was operationally defined as reportedly consuming study drug for at least 80% of assigned days.[29] Pill and patch counts were conducted at each study visit to confirm reported treatment compliance. The two efficacy outcome measures were continuous abstinence (CA) for the last 4 weeks of active treatment (CA weeks 9–12) and for the last 16 weeks of study participation (CA weeks 9–24). CA at weeks 9–12 and 9–24 was contingent upon both self-reported abstinence and exhaled carbon monoxide values less

than 10 parts per million. Participants who withdrew prior to study completion or who were lost to follow-up were considered smoking.

Data Analytic Plan

All analyses were conducted in SAS version 9.4 (Cary, NC). To investigate MM within the EAGLES study, participants enrolled in the PC were categorized into one of three groups based on the number of SCID-verified primary and comorbid diagnoses at baseline: one diagnosis or primary only (PO), two diagnoses or psychiatric CM, or three or more diagnoses or psychiatric MM.

Differences in demographic, baseline psychiatric, and baseline smoking-related characteristics across diagnostic grouping were identified simplistically via nominal p values from either chi-square analyses (categorical) or analyses of variance (numerical).

Occurrence (presence or absence) of a treatment-emergent, moderate-to-severe NPSAE was analyzed with a generalized linear regression model (binomial distribution with identity link to yield risk differences) having terms representing treatment randomization (four levels: varenicline, bupropion, NRT, and placebo), diagnostic grouping (three levels: PO, CM, and MM), region (two levels: US and non-US), and the interaction between treatment and diagnostic grouping. This model is referred to as the basic statistical model. Here, region of enrollment was a stratification factor in the trial and was included in the model because of its previously established association with mental health symptom severity in a related varenicline study[41] and with smoking cessation outcomes in the EAGLES trial.[42]

Treatment compliance (yes or no) was analyzed via a stepwise logistic regression analysis (with 10% entry and 20% stay thresholds) employing forced inclusion of the basic statistical model and subsequent evaluation of a candidate list consisting of 39 baseline covariates that reflected demographic (eg, age, gender, race), smoking-related (eg, FTCD, cigarettes per day, years spent smoking), and psychiatric factors (eg, HADS, CGI-S, use of psychotropic medication).

CA at weeks 9–12 (yes or no) was analyzed using a logistic regression with the same basic statistical model as before. This approach was then repeated for CA at weeks 9–24 (yes or no).

Regression summaries include type 3 model p values and Tukey–Kramer adjusted 95% confidence intervals (CIs) for effect size estimates (either risk difference or odds ratio [OR]). Treatment by diagnostic grouping estimates were computed via an analysis of simple effects (ie, slice by treatment).

Results

Descriptive Statistics and Demographic and Baseline Differences

Table 1 presents descriptive statistics stratified by diagnostic grouping for baseline demographic, smoking, and psychiatric characteristics. Supplementary Figure 1 shows rates of co-occurring PD and SUD in the CM (panel A) and MM groups (panel B), stratified across primary psychiatric diagnosis. Overall, 63.8% of participants (n = 2618) were classified as having only a primary psychiatric diagnosis and placed in the PO group, 20.9% (n = 859) were categorized into the CM group, and 15.3% (n = 626) were categorized into the MM group. In all three groups, the most common category of primary psychiatric diagnosis was mood disorders (73.2% PO, 66.6% CM, 66.8% MM), and anxiety disorders represented the second most common primary diagnosis in all three groups (17.1% PO, 22.4% CM, 23.6% MM). Psychotic disorders (9.4% PO, 10.0% CM, 8.9% MM) and borderline personality disorder (0.3% PO, 0.0% CM, 0.6% MM) were less common primary psychiatric diagnoses.

In the CM and MM groups, alcohol and SUDs were the most common class of co-occurring mental health diagnosis (51.3% CM, 80.2% MM), followed by anxiety disorders (26.8% CM, 46.8% MM). Of note, regardless of treatment condition, diagnostic grouping was associated with permanent discontinuation of treatment (24.8% PO, 27.5% CM, 30.0% MM, p = .02) and with being lost to follow-up (5.8% PO, 7.6% CM, 9.1% MM, p < .01).

Results in Table 1 suggest broad differences across groups. From a demographic perspective, the CM and MM cohorts were associated with male gender, older age, nonwhite race or ethnicity, higher body mass index, living in the US, and a greater number of medical comorbidities. When considering baseline smoking characteristics, the CM and MM cohorts were associated with higher dependence, a greater number of previous quit attempts, and greater prior use of pharmacotherapy for smoking cessation (eg, varenicline, bupropion, and NRT). Finally, when evaluating baseline psychiatric factors, the CM and MM cohorts were associated with more frequent use of antidepressant, anxiolytic, antipsychotic, and mood-stabilizing medications, as well as more frequent suicidal ideation and behavior, more severe global psychiatric impairment, and more severe symptoms of depression, anxiety, and aggression.

Incidence of Moderate-to-Severe NPSAEs

Table 2 reports results from the regression analysis evaluating the impact of psychiatric CM and MM on developing moderate-to-severe NPSAEs during the EAGLES trial. There was no evidence of an interaction between diagnostic grouping and treatment condition (p = .96), nor was there a main effect of either treatment condition (p = .45) or region (p = .48). Diagnostic grouping was a significant predictor (p < .01), having least square mean estimated NPSAE rates of 4.6%, 5.1%, and 11.9% for PO, CM, and MM, respectively. Tukey–Kramer adjusted pairwise comparisons demonstrated that the MM cohort had a significantly higher incidence of moderate-to-severe NPSAEs than either the CM cohort (risk difference = 6.8%, 95% CI = 3.3%, 10.4%) or the PO cohort (risk difference = 7.3%, 95% CI = 4.0%, 10.5%), with the CM and PO cohorts showing similar rates of NPSAEs (risk difference = 0.4%, 95% CI = –1.6%, 2.5%).

Effects on Treatment Adherence and Cessation Efficacy

Tables 3 and 4 report results from regression analyses conducted to determine the impact of mental health CM and MM on smoking cessation pharmacotherapy compliance and efficacy, respectively. Observed rates of treatment compliance were 79.1%, 76.9%, and 75.0% for the PO, CM, and MM cohorts, respectively. In the initial stepwise regression model, all four forced inclusion predictor terms (randomized treatment, diagnostic grouping, region, and treatment by diagnosis interaction) were insignificant. Subsequently, 13 baseline covariates (listed in Table 3) were sequentially added to produce the final model. The additional covariates in the model (particularly noting the presence of psychotropic or psychiatric medication variables, quantification of medical comorbidities, and various mental health assessments) have shown better explanatory value than that from diagnostic grouping, where ORs became numerically closer to

Table 1. Demographic and Baseline Characteristics Stratified Across Number of Psychiatric Diagnoses

		# Present psychiatric and/or substance use disorders			
	Total sample (n = 4103)	Primary only (n = 2618)	Comorbidity (n = 859)	Multimorbidity (n = 626)	p
Demographic characteristics					
Sex					<.01*
Male	1565 (38.1)	933 (35.6)	360 (41.9)	272 (43.5)	
Female	2538 (61.9)	1685 (64.4)	499 (58.1)	354 (56.5)	
Age (years)	47.1 (11.8)	47.4 (11.9)	46.9 (11.5)	45.7 (11.2)	<.01*
Race or ethnicity					<.01*
White	3313 (80.7)	2192 (83.7)	662 (77.1)	459 (73.3)	
Black	647 (15.8)	356 (13.6)	159 (18.5)	132 (21.1)	
Other	142 (3.5)	70 (2.7)	38 (4.4)	34 (5.4)	
Body mass index (kg/m^2)	28.6 (6.6)	28.1 (6.4)	29.1 (6.6)	29.9 (7.1)	<.01*
Region of enrollment					<.01*
US	2355 (57.4)	1345 (51.4)	551 (64.1)	459 (73.3)	
Non-US	1748 (42.6)	1273 (48.6)	308 (35.9)	167 (16.7)	
Number of medical comorbidities	7.7 (6.1)	6.4 (5.6)	8.7 (5.7)	11.7 (6.5)	<.01*
Smoking characteristics					
FTCD	6.0 (2.0)	5.9 (2.0)	6.1 (1.9)	6.3 (1.9)	<.01*
Duration of smoking (years)	28.5 (11.9)	28.5 (12.0)	28.9 (12.0)	28.4 (11.6)	.64
Cigarettes per day	20.7 (8.4)	20.6 (8.3)	20.8 (8.5)	20.7 (8.6)	.83
# Previous quit attempts	3.5 (8.0)	3.0 (4.7)	3.9 (12.1)	4.7 (10.9)	<.01*
Prior smoking cessation medications					
Varenicline	659 (16.1)	363 (13.9)	160 (18.6)	136 (21.7)	<.01*
Bupropion	407 (9.9)	225 (8.6)	96 (11.2)	86 (13.7)	<.01*
Nicotine replacement therapy	1095 (26.7)	596 (22.8)	264 (30.7)	235 (37.5)	<.01*
Psychiatric characteristics					
HADS score					
Anxiety subscale	5.2 (3.9)	4.6 (3.7)	5.6 (3.9)	6.8 (4.2)	<.01*
Depression subscale	3.2 (3.3)	3.0 (3.1)	3.4 (3.4)	4.1 (3.7)	<.01*
BPAQ total score	58.7 (18.6)	57.1 (17.9)	60.3 (19.0)	63.4 (19.6)	<.01*
C-SSRS					
History of suicidal ideation	1373 (33.8)	698 (26.9)	346 (40.9)	329 (53.2)	<.01*
History of suicidal behavior	513 (12.6)	235 (9.1)	130 (15.3)	148 (23.9)	<.01*
Psychotropic medications at enrollment					
Any	1992 (48.5)	1243 (47.5)	439 (51.1)	310 (49.5)	.16
Antidepressant	1374 (33.5)	839 (32.0)	313 (36.4)	222 (35.5)	.03*
Anxiolytic	621 (15.1)	346 (13.2)	158 (18.4)	117 (18.7)	<.01*
Antipsychotic	651 (15.9)	371 (14.2)	157 (18.3)	123 (19.6)	<.01*
Mood stabilizers	82 (2.0)	31 (1.2)	28 (3.3)	23 (3.7)	<.01*
Clinical Global Impressions—Severity					<.01*
Normal-not at all ill	2075 (50.6)	1521 (58.1)	350 (40.7)	204 (32.6)	
Borderline-mentally ill	814 (19.8)	487 (18.6)	206 (24.0)	121 (19.3)	
Mildly ill	930 (22.7)	504 (19.3)	233 (27.1)	193 (30.8)	
Moderately ill	275 (6.7)	101 (3.9)	68 (7.9)	106 (16.9)	
Markedly ill	1 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	

Summary statistics are based on all randomized participants in the psychiatric cohort of the EAGLES study (n = 4103). Values reflect number (percentage) or mean (standard deviation). Chi-square analyses were conducted for categorical outcomes, while ANOVA F tests were conducted for continuous outcomes. p values are considered nominal. ANOVA = Analysis of variance, BPAQ = Buss–Perry Aggression Questionnaire, C-SSRS = Columbia Suicide Severity Rating Scale, EAGLES = Evaluating Adverse Events in a Global Smoking Cessation Study, FTCD = Fagerström Test for Cigarette Dependence, HADS = Hospital Anxiety and Depression Scale.

*p < .05.

1 (eg, MM versus PO increased from .80 to .92) and the type 3 p value increased from .08 to .73.

Regarding treatment efficacy, the observed CA rates for weeks 9–12 and 9–24 were 20.8% and 14.1% for the PO cohort, 19.9% and 13.0% for the CM cohort, and 17.3 and 10.2 for the MM cohort. Based on the logistic regression of CA at weeks 9–12, there was no evidence of an interaction between diagnostic grouping and treatment condition (p = .21), nor was there a main effect of diagnostic grouping (p = .52). Treatment condition (p < .01) and region (p < .01) were both significant terms. Tukey–Kramer adjusted pairwise comparisons for MM versus CM (OR = 0.86, 95% CI = 0.61, 1.22) and MM versus PO (OR = 0.87, 95% CI = 0.64, 1.17) suggested similarity for efficacy at weeks 9–12 for the diagnostic grouping.

Similarly, for CA at weeks 9–24, there was again no evidence of an interaction between diagnostic grouping and treatment condition (p = .27), nor a main effect of diagnostic grouping on CA rates (p = .25). Treatment condition (p < .01) and region (p < .01) were both significant terms in this regression as well. Here, Tukey–Kramer adjusted pairwise comparisons again indicated that MM versus CM (OR = 0.78, 95% CI = 0.52, 1.17) and MM versus PO (OR = 0.78, 95% CI = 0.55, 1.12)

Table 2. Generalized Linear Model Evaluating Predictors of Neuropsychiatric Adverse Events

Term	*p*	RD (95% CI) (%)
Treatment	.45	
Varenicline–placebo		2.1 (−1.8, 6.0)
Bupropion–placebo		1.6 (−2.1, 5.3)
NRT–placebo		0.5 (−3.1, 4.0)
Cohort	<.01	
MM–CM		6.8 (3.3, 10.4)
MM–PO		7.3 (4.0, 10.5)
CM–PO		0.4 (−1.6, 2.5)
Region	.48	
Non-US–US		−0.5 (−1.9, 0.09)
Cohort × Treatment	.96	
Varenicline		
MM–CM		6.8 (−1.0, 14.6)
MM–PO		8.3 (1.3, 15.3)
CM–PO		1.5 (−3.0, 6.0)
Bupropion		
MM–CM		5.0 (−2.1, 12.2)
MM–PO		6.1 (−0.2, 12.3)
CM–PO		1.0 (−3.5, 5.6)
NRT		
MM–CM		7.4 (0.7, 14.1)
MM–PO		7.4 (1.3, 13.6)
CM–PO		0.0 (−3.6, 3.7)
Placebo		
MM–CM		8.0 (1.3, 14.8)
MM–PO		7.3 (1.0, 13.6)
CM–PO		−0.8 (−4.2, 2.6)

CI = confidence interval, CM = comorbidity, EAGLES = Evaluating Adverse Events in a Global Smoking Cessation Study, MM = multimorbidity, PO = primary only, RD = risk difference. Based on all randomized and treated participants in the psychiatric cohort of the EAGLES study (n = 4061).

showed similar relationships to efficacy at weeks 9–24. It should be noted that the significance of treatment condition in both regression models is consistent with results from the parent study.[29]

Discussion

The purpose of this analysis was to evaluate the prevalence of mental health CM and MM among smokers in the EAGLES trial, as well as the extent to which CM and MM were associated with demographic and baseline differences, development of NPSAEs, successful treatment compliance, and successful smoking cessation. The inclusion and exclusion criteria for EAGLES facilitated enrollment of smokers with multiple lifetime mental health conditions. Thus, data from the parent trial are uniquely suited to answer these important smoking-related questions about mental health CM and MM. Results indicated that smokers with mental health CM and MM presented to the EAGLES trial with different demographic, medical, psychiatric, and smoking-related profiles than smokers with only one psychiatric diagnosis, and attrition from the study seemed to be associated with increasing psychiatric complexity. Results also indicated that, as compared with smokers with only one primary or a primary and secondary diagnosis, smokers with psychiatric MM were at elevated risk for developing NPSAEs when making a quit attempt using smoking cessation pharmacotherapies. However, there was no evidence that mental health CM or MM served as barriers for treatment adherence or smoking cessation, in general or within specific medication conditions.

These results extend previously published findings from the EAGLES trial regarding prediction of NPSAEs[43] and successful smoking cessation[42] among smokers with psychiatric conditions. These studies found that symptom severity and specific PDs were associated with greater likelihood for neuropsychiatric events and reduced likelihood for smoking cessation, respectively. Taken together, our results extend these findings and suggest that a more complex clinical presentation may be more closely associated with adverse events during the quit process than with unsuccessful cessation among smokers using pharmacotherapy to quit. Indeed, the incidence of moderate-to-severe NPSAEs in the MM cohort was more than twice that of the CM and PO cohorts. This is noteworthy given that over one-fifth of the sample considered met diagnostic criteria to be classified into the MM cohort upon enrolling in the study. Future research could target-specific populations of smokers exhibiting psychiatric CM and MM, such as those with co-occurring PD and SUD or with co-occurring mood and anxiety disorders.

These findings also reinforce several important elements of clinical practice regarding the utility of smoking cessation pharmacotherapies among populations with mental health conditions. First, one of the parent study's main conclusions was that smoking cessation pharmacotherapies are well tolerated and efficacious in psychiatrically stable smokers.[29] Our findings support this assertion and extend it by demonstrating that, when compared with a single psychiatric diagnosis, mental health CM and MM were not associated with treatment noncompliance or reduced treatment efficacy, regardless of the type of medication being considered. That said, mental health CM and MM were associated with permanent dropout from the study and being lost to follow-up. These associations suggest that in future pharmacotherapy randomized controlled trials, enhanced retention efforts should be implemented to retain smokers with complex clinical mental health and substance use presentations, and exploring potential replication of these relationships through other methods of assigning smoking status beyond an intent-to-treat approach would be valuable.

Second, individuals with PD and SUD comprise health disparity populations that experience higher rates of smoking, decreased rates of successful cessation, and higher rates of tobacco-related morbidity, mortality, and disease development.[44–46] The results reported here support these trends and demonstrate that, when compared with smokers with only one psychiatric condition, smokers with mental health CM and MM are more likely to be of minority race or ethnicity, to have more complex medical histories, to have made a greater number of previous quit attempts, and to endorse higher levels of cigarette dependence. The stepwise regression results also indicate that, if structured diagnostic interviews are not available to identify mental health CM and MM in smokers attempting to quit, then less burdensome self-report measures of constructs like suicidality, anxiety, aggression, and psychotropic medication use can be utilized to conceptualize the psychiatric complexity and instability that defines this population. It is possible that our estimates of CM and MM were actually underestimates, as well, since acute psychiatric instability and meeting diagnostic criteria for an active SUD were exclusion criteria for EAGLES.

Finally, Prochaska[15] suggested the integration of mood management strategies and more frequent patient follow-up for providers assisting psychiatrically ill smokers with a quit attempt. The data described here support this recommendation, as mental health MM was not only associated with a higher number of prior smoking cessation

Table 3. Stepwise Logistic Regression Results Evaluating Prediction of Treatment Compliance

			Initial model		Final model
Term			*p*	OR (CI)	*p*	OR (CI)
Treatment			.13		.06	
Varenicline–placebo				1.24 (0.89, 1.71)		1.27 (0.91, 1.76)
Bupropion–placebo				1.16 (0.85, 1.60)		1.20 (0.87, 1.66)
NRT–placebo				1.33 (0.96. 1.83)		1.40 (1.01, 1.94)
Cohort			.08		.73	
MM–CM				0.91 (0.68, 1.22)		0.98 (0.73, 1.34)
MM–PO				0.80 (0.62, 1.03)		0.92 (0.70, 1.23)
CM–PO				0.88 (0.70, 1.10)		0.94 (0.74, 1.19)
Region			.93		.95	
Non-US–US				0.99 (0.85, 1.16)		1.01 (0.85, 1.19)
Cohort × Treatment			.88		.82	
Varenicline						
MM–CM				1.02 (0.56, 1.88)		1.19 (0.64, 2.23)
MM–PO				0.89 (0.53, 1.49)		1.02 (0.59, 1.76)
CM–PO				0.87 (0.55, 1.35)		0.85 (0.54, 1.35)
Bupropion						
MM–CM				0.69 (0.39, 1.23)		0.78 (0.43, 1.40)
MM–PO				0.65 (0.41, 1.04)		0.77 (0.47, 1.26)
CM–PO				0.94 (0.59, 1.49)		0.99 (0.61, 1.58)
NRT						
MM–CM				0.95 (0.53, 1.72)		1.01 (0.55, 1.85)
MM–PO				0.90 (0.54, 1.49)		1.10 (0.64, 1.87)
CM–PO				0.94 (0.60, 1.49)		1.09 (0.69, 1.74)
Placebo						
MM–CM				1.00 (0.57, 1.76)		1.00 (0.56, 1.79)
MM–PO				0.79 (0.48, 1.28)		0.85 (0.51, 1.42)
CM–PO				0.79 (0.52, 1.20)		0.85 (0.55, 1.31)
Covariates (at baseline)	Unit	Entry	Entry *p*	*p*	OR (CI)	
Start age	10 years	1	<.01	<.01	1.47 (1.25, 1.73)	
C-SSRS suicidal ideation	Yes or no	2	<.01	<.01	0.76 (0.65, 0.90)	
Years smoking	10 years	3	<.01	<.01	1.14 (1.06, 1.22)	
NRT prior use	Yes or no	4	<.01	<.01	0.78 (0.65, 0.93)	
Any anxiolytic, sedative, or hypnotic	Yes or no	5	<.01	<.01	0.63 (0.50, 0.80)	
BPAQ hostility	10 scale units	6	<.01	<.01	1.28 (1.12, 1.47)	
HADS anxiety	1 scale unit	7	<.01	<.01	0.97 (0.94, 0.99)	
Cigarettes per day	10 (count)	8	.01	<.01	0.88 (0.80, 0.96)	
Any psychotropic medication	Yes or no	9	.02	<.01	1.54 (1.17, 2.03)	
Gender	Female or male	10	.06	.04	0.84 (0.72, 0.99)	
No. medical comorbidities	5 (count)	11	.05	.03	1.09 (1.01, 1.18)	
Any psychiatric medication	Yes or no	12	.06	.06	0.78 (0.60, 1.01)	
CGI-S	Ordinal scale	13	.09	.10		
Borderline–normal					1.21 (0.97, 1.51)	
Mild–normal					0.87 (0.71, 1.06)	
Moderate–normal					0.94 (0.68, 1.30)	

BPAQ = Buss–Perry Aggression Questionnaire, CGI-S = Clinical Global Impression—Severity, CI = 95% confidence interval, CM = comorbidity, C-SSRS = Columbia Suicide Severity Rating Scale, EAGLES = Evaluating Adverse Events in a Global Smoking Cessation Study, FTCD = Fagerström Test for Cigarette Dependence, HADS = Hospital Anxiety and Depression Scale, MM = multimorbidity, NRT = nicotine replacement therapy, OR = odds ratio, PO = primary only. Based on all randomized and treated participants in the psychiatric cohort of the EAGLES study (n = 4061). Baseline covariates considered but not included in stepwise model development were race or ethnicity, history of alcohol abuse, history of substance use, a combined alcohol or substance use history, C-SSRS suicidal behavior, C-SSRS suicidal ideation or behavior, use of any psychotropic medication (overall and for antidepressants, antipsychotics, mood stabilizers, or other psychotropic medications), history of varenicline use, history of bupropion use, comorbid medical diagnoses (both presence and number), living with a smoker, contact with smokers, history of serious quit attempt, FTCD, body mass index, weight, HADS depression score, and BPAQ (total score and its physical, verbal, and anger subscores).

attempts, but also a greater likelihood of developing a NPSAE when taking a smoking cessation pharmacotherapy. Clinicians who are treating smokers with psychiatric conditions who are trying to quit are thus encouraged to closely monitor their patients, to plan for changes in psychiatric symptoms during quit attempts, and to inform their patients about these expectations, especially if their patients are

Table 4. General Linear Model Evaluating Predictors of Continuous Abstinence From Smoking at Weeks 9–12 and 9–24

	Weeks 9–12		Weeks 9–24	
Term	*p*	OR (95% CI)	*p*	OR (95 %CI)
Treatment	<.01		<.01	
Varenicline–placebo		3.59 (2.41, 5.34)		2.23 (1.39, 3.58)
Bupropion–placebo		1.82 (1.20, 2.78)		1.65 (1.02, 2.67)
NRT–placebo		2.15 (1.43, 3.24)		1.74 (1.09, 2.77)
Cohort	.52		.25	
MM–CM		0.86 (0.61, 1.22)		0.78 (0.52, 1.17)
MM–PO		0.87 (0.64, 1.17)		0.78 (0.55, 1.12)
CM–PO		0.82 (0.79, 1.29)		1.00 (0.75, 1.33)
Region	<.01		<.01	
Non-US–US		1.75 (1.49, 2.05)		1.68 (1.39, 2.02)
Cohort × Treatment	.21		.27	
Varenicline				
MM–CM		0.73 (0.42, 1.29)		0.52 (0.24, 1.12)
MM–PO		0.99 (0.60, 1.62)		0.53 (0.27, 1.05)
CM–PO		1.34 (0.90, 2.01)		1.03 (0.64, 1.65)
Bupropion				
MM–CM		0.80 (0.41, 1.58)		1.05 (0.48, 2.30)
MM–PO		0.68 (0.38, 1.21)		0.75 (0.40, 1.43)
CM–PO		0.85 (0.52, 1.38)		0.72 (0.40, 1.28)
NRT				
MM–CM		1.43 (0.78, 2.64)		1.17 (0.57, 2.41)
MM–PO		1.17 (0.71, 1.93)		1.13 (0.62, 2.08)
CM–PO		0.82 (0.51, 1.32)		0.97 (0.56, 1.69)
Placebo				
MM–CM		0.66 (0.28, 1.56)		0.58 (0.22, 1.53)
MM–PO		0.73 (0.34, 1.56)		0.82 (0.34, 1.97)
CM–PO		1.10 (0.62, 1.95)		1.41 (0.75, 2.64)

CI = 95% confidence interval, CM = comorbidity, EAGLES = Evaluating Adverse Events in a Global Smoking Cessation Study, MM = multimorbidity, NRT = nicotine replacement therapy, OR = odds ratio, PO = primary only. Based on all randomized participants in the psychiatric cohort of the EAGLES study (n = 4103).

taking smoking cessation pharmacotherapies alongside other psychotropic medications.

These results should be interpreted within the context of important limitations, many of which have already been mentioned. First, participants with psychiatric diagnoses were considered stable upon enrollment into the study; thus, our results may not generalize to smokers with untreated, emergent, or symptomatically unstable psychiatric conditions. Second, individuals with active SUDs or with high risk of suicide were excluded from participation, further restricting potential generalizability to more complex psychiatric populations. Additional research is needed to evaluate whether these relationships would hold among those with less stable and/or more active symptoms. Third, the region of enrollment predictor, which was a US or non-US two-level factor, may not adequately account for nuanced differences in rates of psychiatric diagnoses across countries in the EAGLES trial. Although this binary categorization approach has been used in other secondary analyses of EAGLES data,[42,43] further research into international differences in the presentation of PDs, SUDs, and mental health CM and MM would be informative. Fourth, psychiatric medication use and histories were most often collected via self-report, which can be associated with inaccuracy or recall bias. Fifth, it is possible that, since there are between-group differences across diagnostic grouping, these factors might better explain differences in experiencing NPSAEs, adhering to study treatment, or successfully quitting smoking than diagnostic grouping itself. Further, unmeasured confounding variables might also bias our results. Finally, given the number of statistical tests conducted to identify demographic, smoking, and psychiatric characteristics, it is possible that between-group differences may have been found due to multiplicity issues.

Despite these limitations, the results confirm that FDA-approved smoking cessation pharmacotherapies are generally well tolerated and effective in smokers with stable psychiatric conditions, including those with more than one psychiatric diagnosis. These data also suggest that psychiatric complexity does not serve as a barrier to successful treatment compliance or treatment efficacy for the medications studied, and providers can feel reasonably confident in prescribing such medications to smokers with mental health conditions. However, given the potential for patients with psychiatric MM to develop NPSAEs when attempting to quit with medications, providers are encouraged to regularly follow-up with such patients when they are making a medication-assisted cessation attempt.

Supplementary Material

A Contributorship Form detailing each author's specific involvement with this content, as well as any supplementary data, are available online at https://academic.oup.com/ntr.

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Declaration of Interests

Given their role in funding the parent study, Pfizer, Inc. was also involved in study design, data collection, and data analyses associated with this manuscript. Authors DL, PAS, and SD are employees of Pfizer, Inc. Author RMA provides consulting and/or advisory board services to Pfizer and receives research support from Pfizer and Embera Neurotherapeutics. Authors JBC, BSM, NG, and ND have no potential conflicts of interest to declare. All authors have had full access to the data described in this study and take full responsibility for the integrity of the data and the accuracy of the data analysis.

Data Availability

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 deidentified 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 US and/or EU or (2) in programs that have been terminated (ie, 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 deidentified 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.

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