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Effects of Varenicline, Depressive Symptoms, and Region of Enrollment on Smoking Cessation in Depressed Smokers

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Abstract

Introduction: Despite effective treatments, relapse to smoking remains a vexing global health problem. One predictor of relapse is depressive symptoms. Medications such as varenicline reduce withdrawal-related symptoms of depression, reducing relapse. This study examined whether varenicline moderated the effect of depressive symptoms on relapse, and whether this varied by region of enrollment.

Methods: Adult smokers ($n = 525$; 37% male) with past or current, stable major depressive disorder recruited from United States ($n = 255$), and European ($n = 270$) sites participated in a randomized, double-blind cessation treatment trial including 12 weeks of varenicline or placebo, with 40-week nontreatment follow-up.

Results: Longitudinal and binary logistic regressions were used to model the probability of sustained abstinence by end of treatment and point-prevalence abstinence in follow-up. The association between depression symptoms and abstinence was moderated by intervention group at end of treatment, and by region during follow-up: more severe symptoms were associated with end-of-treatment relapse for placebo (odds ratio [OR] = 0.91, $p = .003$), but not varenicline (OR = 0.99, $p = .568$). During follow-up, increased symptoms of depression predicted greater likelihood of smoking for European ($p = .009$) but not US participants. Europeans were more likely to be abstinent for both outcomes ($p < .01$).

Conclusions: These results extend studies demonstrating varenicline is associated with less withdrawal-related depression, and suggest it aids cessation even in smokers with depressive symptoms. Findings also suggest regional differences in the relationship between depressive symptoms and cessation that may be related to differences in prevalence.

Implications: This study indicates varenicline may aid cessation partially by reducing withdrawal-related symptoms of depression. It also suggests that the impact of depressive symptoms on cessation varies regionally, and that this variation may be related to differences in smoking prevalence.

Introduction

Tobacco use is the most significant contributor to preventable illness and death worldwide, and is associated with an estimated 5 million deaths annually; current trends suggest this will increase by 60% by 2030.[1–3] The majority of smokers report a desire to quit, and up to half make a quit attempt in any given year, but the vast majority of quit attempts are unsuccessful.[4,5] Thus, identifying interventions that reduce relapse risk is a global public health priority.

Depressive symptoms are one of the strongest predictors of a failed quit attempt. Individuals with current or past depression are at increased risk of smoking,[6] and both state (eg, withdrawal-related) and trait (eg, depression proneness) negative moods are associated with greater risk of relapse.[6–8] Pharmacological cessation aids appear to reduce symptoms of depression or negative affect related to withdrawal, at least in samples of smokers excluding psychiatric and substance use comorbidity[9,10]; however, one recent study indicates this may not be the case among substance abusers.[11] To the extent that these aids mitigate depressive symptoms, they presumably enhance the odds of successfully quitting. Such assistance may be particularly important for smokers with current or past depression who are vulnerable to negative moods and who experience more severe withdrawal symptoms during a quit attempt.[12,13] In support of this hypothesis, we recently reported that smokers with stable depression treated with varenicline were more than twice as likely as those receiving placebo to maintain abstinence for 52 weeks postquit.[14]

Smoking cessation and relapse rates might also vary geographically. The hardening hypothesis[15,16] suggests that as smoking prevalence declines as it has in high income countries such as the United States and United Kingdom, remaining smokers are more likely to possess characteristics (eg, depression, more severe nicotine dependence) that heighten the difficulty of cessation. Thus, the statistical effect of depressive symptoms on cessation success may be reduced as a function of lower variability in depressive symptoms in these countries. From this perspective, the negative impact of depressive symptoms on cessation may be more readily detected in countries where smoking is more common.

Population-level data on the hardening hypothesis with respect to depression symptoms are mixed, with some studies suggesting that depressed smokers are increasingly unlikely to quit[17] and others finding no change.[16,18] While the prevalence of smoking worldwide has generally declined over the past 15 years, trends vary considerably across geographical boundaries. Data from 2010[19,20] indicated current adult prevalence of approximately 19% in the United States and 27% in 18 European countries, with rates for individual countries ranging from 16% to 41%. Countries with a higher proportion of current smokers tended to have less restrictive tobacco-related regulation, and to have populations with lower income and less education. Interestingly, within countries, the prevalence of smoking does not appear to be related to the proportion of heavily dependent smokers, particularly for men.[21] Recent evidence also indicates that use of cessation aids is more common in countries with more extensive anti-tobacco programs,[22] regardless of individual education or socioeconomic status. Despite these differences, to our knowledge there has been little examination of whether the efficacy of cessation interventions in randomized controlled trials may differ between countries. Furthermore, to the best of our knowledge, no previous studies have directly examined whether the impact of depressive symptoms on smoking cessation also varies geographically.

The current study was a secondary analysis of data from a recent trial of varenicline as a cessation aid for US and European smokers with either past or current, stable major depression.[14] The a priori goal of this study was to extend our initial findings by assessing the impact of baseline depressive symptoms on short- and long-term cigarette abstinence, and the effect of varenicline versus placebo on this relationship. We expected that participants with more severe baseline symptoms of depression would be less likely to quit smoking, but that this effect would be mitigated by varenicline compared with placebo. Secondarily, we sought to evaluate whether the effects of varenicline and depression symptoms on cessation differed by region (United States vs. Europe). Given the findings of Fernández et al.[21] that national prevalence was not associated with dependence severity, we hypothesized that overall cessation rates and differences between the varenicline and placebo groups would be unrelated to region of enrollment. Due to the lack of previous studies, we made no specific hypotheses regarding regional differences in the association between depressive symptoms and cessation.

Method

Overview

The present study was a secondary analysis of a phase 4, double-blind, randomized controlled trial comparing 12 weeks of varenicline, 1 mg twice daily, versus placebo in a sample of smokers with current stable or past major depression.[14] The parent study was conducted over 2 years in a total of 38 centers in eight countries; 48.6% (n = 255) participated at sites in the United States, and 51.4% (n = 270) at European Union (EU) sites (Table 1). Participants provided written informed consent before completing any assessments; the study protocol was approved by institutional review boards or independent ethics committees at each site, and the trial adhered to the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines.

Participants were recruited through television, radio, and newspaper advertisements or from clinics associated with some study sites. Eligibility criteria included being 18–75 years old, motivated to quit smoking, smoking ≥10 cigarettes per day, and an exhaled carbon monoxide level >10 ppm at screening. Exclusion criteria included current or past 6 months diagnosis of dementia, psychotic disorders, bipolar disorders, or severe personality disorders; high suicide or homicide risk; and past 30-day use of bupropion, nortriptyline, mania or psychosis medications or investigational drugs, or any past use of varenicline. Users of other nicotine products and marijuana were also excluded.

Interventions and Psychiatric Rating Scales

Participants received blinded medication bottles and were titrated to a full dose (1 mg twice a day) of either varenicline or placebo during the first week. Participants were instructed to choose day 8 of study participation as their target quit date. In addition to medication, participants also received brief (10 minutes or less) manualized smoking cessation counseling from baseline through week 52. The counseling was done in accordance with the guidelines set forth by the Agency for Healthcare Research and Quality.[23] The Fagerström Test for Nicotine Dependence (FTND[24]) was used to measure baseline tobacco dependence; the FTND is a self-report measure with a possible score range of 1–10. Scores of 6 or more are thought to indicate more severe dependence.[25] Internal consistency was relatively low in the current sample (Cronbach's α = 0.52), consistent with previous studies.[24,26] Depressive symptoms were measured at baseline using the Montgomery-Asberg Depression Rating Scale (MADRS[27]). The MADRS consists of 10 items that were rated by a clinician on a 7-point scale, with higher scores indicating greater severity in the past 2 weeks. Internal consistency was excellent in this sample (α = 0.88). Possible MADRS scores range from 0 to 60; we considered values greater than 11 to indicate a current depressive episode.[14,27] As shown in Table 1, 136 participants (25.9%) had baseline scores >11.

Outcomes and Efficacy

Participants attended weekly clinic and intermittent telephone visits over a total of 52 weeks, including 12 weeks of treatment and 40 weeks of follow-up. Two smoking outcomes were calculated. First, we determined

whether participants had achieved continuous abstinence (ie, no smoking) for 4 weeks, from week 9 to the end of treatment at week 12. Second, we assessed past-week 7-day point prevalence abstinence during the post-treatment follow-up at weeks 13, 14, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52. Outcomes were assessed via self-report, confirmed by expired carbon monoxide (≤10 ppm) during in-person visits.

Statistical Analysis

Analyses included all participants who received at least one dose of study medication. Prior to hypothesis testing, we examined bivariate associations between demographic variables and our primary variables of interest. Given that the parent trial was focused on smokers with stable or past depression, and that 72% of participants were taking antidepressants at study initiation, all analyses included concomitant antidepressant status as a covariate. Nicotine dependence severity (ie, FTND score) was also included in each model. The effects of baseline depressive symptoms (MADRS score, mean-centered at 0), treatment (varenicline vs. placebo), region (US vs. EU), and their interactions on continuous abstinence during weeks 9–12 were assessed via binary logistic regression. The effects of the same predictors on 7-day point prevalence abstinence over time during weeks 13–52 were tested using longitudinal logistic regression via the generalized estimating equations (GEE) procedure[28] using SAS PROC GENMOD. The GEE method estimates model parameters using all available data, rather than excluding cases with missing data listwise or requiring deterministic assumptions (eg, that missing data equal relapse), approaches which have been shown to introduce bias and which are inconsistent with some recommendations for reporting of clinical trials.[29,30] More sophisticated approaches (ie, multiple imputation), while preferable to deterministic methods, also introduce measurement error, and studies indicate that this may counterbalance improvements in accuracy of parameter estimation.[31] GEE also assumes that data are missing at random, after adjusting for the covariates included in the model. In the current sample, neither the proportion of missing assessments during weeks 13–52, nor whether participants had any missing data during this period, was associated with treatment group, region of enrollment, baseline depressive symptoms, or 4-week continuous abstinence during weeks 9–12. GEE models are robust to misspecification of the dependency structure that may result when individuals provide repeated data over time.[32] This model characterized smoking status over time in terms of initial (week 13) smoking status and time-related changes in smoking status. The model initially included time and time^2 terms, as well as interactions between time and baseline depression symptoms, treatment, and region, to allow for curvilinear trends over time. Due to recent reports of potential sex differences in varenicline use and efficacy,[33,34] initial models tested for sex by treatment group interactions. For both analyses, nonsignificant interaction terms were removed in a backward manner, and the models re-fit. For all hypothesis tests, $\alpha = .05$.

Results

Preliminary Analyses

Demographic and clinical characteristics are shown in Table 1 by treatment group and region of enrollment. EU participants were significantly more likely to be male, and tended to have lower baseline depression scores than their US counterparts. US participants in the placebo group smoked significantly fewer cigarettes per day than those in the EU placebo group, but neither was significantly different from the US or EU varenicline groups. There were no differences by treatment or region in terms of age, nicotine dependence severity, duration of smoking career, or concomitant antidepressant status.

Table 1. Demographic and Clinical Characteristics

	United States		Europe	
Characteristic	Varenicline (*n* = 126)	Placebo (*n* = 129)	Varenicline (*n* = 130)	Placebo (*n* = 140)
Sex, *n* (%)				
Male	37 (29.4)[a]	40 (31.0)[a]	60 (46.2)[b]	59 (42.1)[b]
Age, y				
Mean (SD)	45.5 (11.3)	46.7(10.5)[a]	45.3 (10.6)[a]	47.5 (11.2)[a]
Range	19–69	20–67	21–73	21–73
FTND				
Mean (SD)	5.8 (1.8)[a]	5.7 (2.0)[a]	5.9 (2.1)[a]	6.1 (2.0)[a]
Range	1–9	1–10	1–10	1–10
Duration of smoking, years				
Mean (SD)	27.4 (11.6)[a]	27.6 (11.7)[a]	24.6 (11.6)[a]	27.1 (11.9)[a]
Range	1–48	3–53	2–55	2–56
Cigarettes/day				
Mean (SD)	17.8 (8.0)[ab]	17.4 (7.9)[a]	18.9 (7.5)[ab]	20.0 (9.1)[b]
Range	2–40	2–50	2–40	2–70
MADRS				
Mean (SD)	8.5 (7.7)[a]	8.7 (8.4)[a]	6.8 (7.0)[b]	7.2 (6.5)[b]
Range	0–37	0–37	0–37	0–23
Current major depressive disorder				
MADRS > 11, *n* (%)	34 (27.0)[ab]	40 (31.0)[a]	26 (20.0)[b]	36 (25.7)[ab]
Antidepressant status				
Yes, *n* (%)	86 (68.3)[a]	88 (68.2)[a]	95 (73.1)[a]	109 (77.9)[a]

Within each variable, values that do not share a superscript were significantly different, $p < .05$. European participants were enrolled at sites in Bosnia and Herzegovina, Croatia, Germany, Hungary, Romania, the Russian Federation, and Spain. FTND, Fagerstrom Test for Nicotine Dependence; MADRS, Montgomery Asberg Depression Rating Scale. Range of possible scores was 0–10 for FTND and 0–60 for MADRS.

Weeks 9–12 Abstinence

As previously described,[14] continuous 4-week end-of-treatment abstinence was achieved by 35.9% of the varenicline group (92/256), compared with 15.6% (42/269) of those randomized to placebo. However, 4-week continuous abstinence rates differed by region: 13.7% of US participants (35/255) versus 36.7% (99/270) of European participants achieved this primary endpoint. The logistic model is shown in Table 2. There were no effects of sex, concomitant antidepressant use, or nicotine dependence on quitting smoking in the short term. The sex × treatment group and MADRS × treatment group × region interactions were not significant, and the terms were not retained in the final model. There was a significant effect of region, such that EU participants were more than four times more likely to achieve continuous abstinence compared with US participants (odds ratio [OR] = 4.08 [95% confidence interval = 2.56% to 6.49%], $p < .001$). There were also significant effects of treatment group (OR = 3.91 [2.54% to 6.34%], $p < .001$) and MADRS × treatment group (OR = 1.08 [1.00% to 1.17], $p = .043$). Given that the MADRS × treatment group interaction was retained in the model, the treatment group main effect indicates that, at the mean level of baseline depressive symptoms, those randomized to varenicline were nearly four times more likely to achieve continuous abstinence than were those randomized to placebo.

To further interpret the MADRS × treatment group interaction, we stratified the sample by treatment group and re-assessed the model. These simple effects analyses indicated that higher baseline symptoms of depression were associated with significantly lower likelihood of abstinence for the placebo group (OR = 0.91 [0.85% to 0.97%], $p = .004$), but not the varenicline group (OR = 0.99 [0.95% to 1.03%], $p = .568$). Among participants randomized to placebo, each one-point increase in baseline MADRS score was associated with a 9% decrease in the odds of abstinence during weeks 9–12. EU participants in both the placebo (OR = 3.63 [1.66% to 7.96%], $p = .001$) and varenicline (OR = 4.36 [2.44% to 7.76%), $p < .001$) groups were approximately four times more likely to quit relative to their US counterparts. Sex was not associated with abstinence in either group.

Weeks 13–52 Abstinence

Point prevalence abstinence rates by treatment group and region are shown in Figure 1. As depicted in Table 3, the primary GEE model of point prevalence abstinence over time yielded a significant main effect of nicotine dependence ($z = -2.43$, $p = .015$), indicating that participants with higher levels of dependence were more likely to be classified as smoking during the 40-week nontreatment follow-up. Sex was not significantly associated with smoking status. All three- and four-way interactions among treatment group, region, baseline depression symptoms, and time were nonsignificant and were not retained in the final model. The sex × treatment group term was also nonsignificant and was not retained. There were significant treatment ($z = 5.88$, $p < .001$) and treatment × time ($z = -3.28$, $p = .001$) effects, indicating an initial advantage of varenicline that faded over time; however, as Figure 1 indicates, treatment with varenicline retained a substantial advantage over placebo, particularly in the EU.

The GEE model also yielded significant region ($z = 4.98$, $p < .001$) and baseline depression × region ($z = -2.10$, $p = .035$) terms. Given the significant interaction, the main effect of region indicates that at the average level of baseline depression symptoms, EU participants were more likely than US participants to be abstinent. To better understand the interaction, we stratified the sample by region and refit the model for each group separately. In the US model, treatment effects mirrored those of the full model, with significant treatment ($z = 3.15$, $p = .002$) and treatment × time ($z = -2.19$, $p = .028$) effects indicating an initial advantage of varenicline versus placebo that weakened over time (ie, relapses to smoking occurred when off treatment). Baseline depression was not associated with smoking status ($z = -0.86$, $p = .390$). The EU model yielded the same pattern of results for treatment group, with an advantage of varenicline at week 13 ($z = 5.12$, $p < .001$) that decreased over time ($z = -2.74$, $p = .006$). However, in contrast to the US model, among EU participants there was a significant effect of baseline depression ($z = -2.62$, $p = .009$). In other words, the impact of baseline depression symptoms on point prevalence abstinence during nontreatment follow-up was moderated by region of enrollment. EU participants' likelihood of abstinence was inversely associated with baseline level of depression, whereas among US participants, abstinence was not significantly related to baseline depression scores. Notably, while these simple effects analyses indicate that the advantage of varenicline versus placebo narrowed over time for both groups, Figure 1 suggests that these changes did not occur simultaneously. For EU participants, the gap between the varenicline and placebo groups narrowed during weeks 12–24, immediately following treatment, and appears stable thereafter. Among US participants, the difference between the two treatment groups was reduced gradually throughout follow-up, with change being most pronounced during weeks 40–52.

Discussion

The goal of this study was to evaluate whether the effect of varenicline on short- and long-term smoking abstinence, as well as the likelihood of relapse, varied as a function of baseline depression symptom severity and the region in which participants were enrolled. As expected, smokers randomized to varenicline were more likely to be abstinent during the final 4 weeks of treatment, regardless of region. Across treatment groups, smokers enrolled in Europe were about four times more likely to be abstinent during this period relative to those enrolled in the US. During the 40-week post-treatment follow-up,

Table 2. Logistic Model of the Odds of Continuous Abstinence, Weeks 9–12

Effect	Coefficient	Standard error	Odds ratio (95% CI)	*p*-Value
Anti-depressant status	−0.11	0.25	0.90 (0.55 to 1.47)	.663
Sex	0.03	0.23	1.03 (0.66 to 1.62)	.884
FTND	−0.10	0.06	0.91 (0.81 to 1.01)	.076
MADRS	−0.10	0.03	0.91 (0.85 to 0.97)	.005
Region	1.41	0.24	4.08 (2.56 to 6.49)	<.001
Treatment	1.36	0.25	3.91 (2.42 to 6.34)	<.001
MADRS × treatment	0.08	0.04	1.08 (1.00 to 1.17)	.042

Sex: 0 = male, 1 = female; Region: 0 = US, 1 = Europe; Treatment: 0 = placebo, 1 = varenicline. Continuous abstinence: 0 = lapse/relapse, 1 = abstinence. FTND, Fagerstrom Test for Nicotine Dependence; MADRS, Montgomery Asberg Depression Rating Scale.

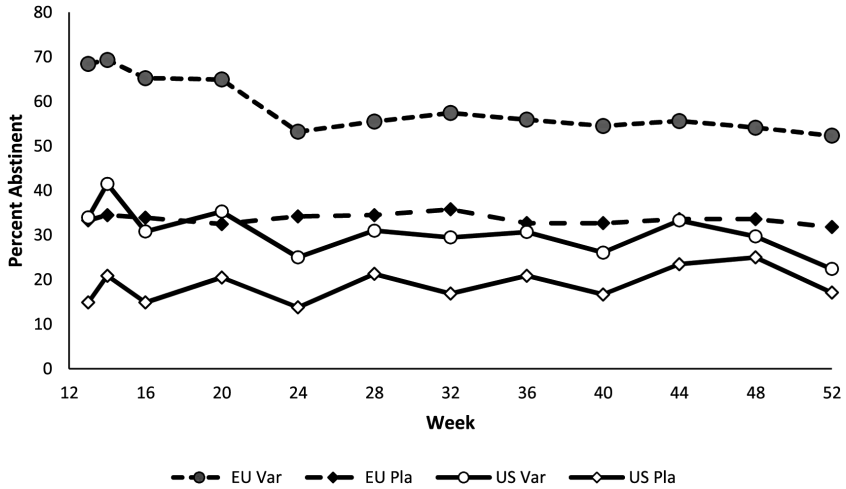

Figure 1. Past week (7-day) point prevalence abstinence rate, weeks 13–52, by treatment and region.

Table 3. GEE Model of the Odds of Point Prevalence Abstinence Over Time, Weeks 13–52

Effect	Coefficient	Standard error	*z*-Score	*p*-Value
Anti-depressant status	0.10	0.22	0.45	.655
Sex	−0.30	0.21	−1.42	.156
FTND	−0.12	0.05	−2.43	.015
MADRS	−0.01	0.02	−0.44	.659
Time	0.01	0.01	0.16	.874
Region	1.48	0.30	4.98	<.001
Treatment	1.39	0.24	5.88	<.001
Treatment × time	−0.02	0.01	−3.28	.001
MADRS × region	−0.06	0.03	−2.10	.035

Sex: 0 = male, 1 = female; Region: 0 = US, 1 = Europe; Treatment: 0 = placebo, 1 = varenicline; point prevalence smoking status: 0 = smoking, 1 = abstinent. FTND, Fagerstrom Test for Nicotine Dependence; MADRS, Montgomery Asberg Depression Rating Scale.

the advantage of varenicline over placebo declined across sites; for EU but not US smokers, randomization to varenicline continued to confer an advantage at the end of follow-up. Smokers experiencing stronger baseline depressive symptoms were less likely to quit smoking than those endorsing lower scores on a valid, reliable mood rating scale. Treatment with varenicline obviated this effect. In contrast, among those receiving placebo, the effect of depressive symptoms was magnified such that an elevated baseline MADRS score was associated with a 9% increase in the odds of lapse or relapse. Once treatment ended, higher levels of depressed mood at baseline predicted return to or continued smoking during the 40-week follow-up period for those treated in Europe and randomized to placebo, but not for other groups. Smoking during follow-up was also positively associated with greater severity of nicotine dependence.

These results are consistent with other research demonstrating that smokers with depressed moods have more difficulty quitting smoking than euthymic individuals,[35–37] and extend our previous finding that varenicline helps smokers with stable depression quit smoking.[14] Regarding the effects of depressive symptoms on quitting, a meta-analysis of smoking cessation trials conducted in smokers with past histories of depression found a 17% reduction in odds of quitting among depressives compared with controls.[6] In another smoking cessation trial in heavy social drinkers, investigators found that several dimensions of depression each independently predicted smoking relapse, and that low positive affect had incremental effects even after controlling for other negative predictors such as severity of nicotine dependence and history of major depression.[38] State or trait depressed mood appear to exacerbate symptoms of nicotine withdrawal.[39]

Although not directly assessed in this study, we speculate that varenicline's efficacy in smokers with depressive symptoms relates to the medication's ameliorative effects on withdrawal-related negative affect, and, possibly, its enhancement of positive affect. These effects may be particularly salient in depression-prone smokers who presumably approach a quit effort with more negative and fewer positive emotions than their nondepressed counterparts. Evidence that varenicline counteracts these effects can be found in both preclinical and clinical studies. For example, varenicline administration lowers intracranial self-stimulation thresholds in rodents, and attenuates the nicotine withdrawal-induced elevations in this biomarker of dysphoria in nicotine-treated rats.[40] In both pooled analyses of varenicline randomized clinical trials in nondepressed smokers,[10,41] and in an independent study[9] comparing this drug with bupropion and placebo, varenicline consistently reduced withdrawal-related symptoms of negative affect compared with placebo. Patterson et al.[42] also demonstrated that varenicline reduced symptoms of negative affect, and raised levels of positive affect, in smokers who underwent a 3-day mandatory abstinence period in the laboratory.

Our finding that smokers enrolled at European sites were more likely to quit smoking and stay quit compared with US enrollees is provocative and bears further exploration. To our knowledge, most multicenter international smoking cessation studies have not formally examined these intercontinental differences despite evidence that smoking cessation varies across countries.[43] For example, surveys conducted in European countries have found country-specific differences in levels of tobacco regulation, social acceptance of smoking, smoking prevalence, and levels of awareness of smoking-related health risks that influence smoking persistence across countries.[20,44] Notably, Eastern European countries and those with lower income levels appear to be at an earlier stage in fighting the tobacco epidemic compared with higher income, more developed, Western European nations. The ongoing, prospective International Tobacco Control Four Country Survey (ITC-4) being conducted in the United Kingdom, US, Australia, and Canada shows that even among higher

income countries there remains a great deal of variability in the levels of quitting activity and the types of supports used.[34,43,45]

The current findings may also provide some insight into one potential source of these regional differences. First, US participants had significantly higher levels of baseline depression symptoms. When baseline depression was controlled for, EU smokers were more likely to be abstinent during long-term follow-up. However, EU smokers with higher baseline depression were less likely to be abstinent, whereas in the US depressive symptoms were unrelated to abstinence during this period. As shown in Table 1, US participants reported more severe depressive symptoms relative to EU participants. Additionally, post hoc analyses revealed that EU participants who achieved 4-week continuous abstinence had lower baseline MADRS scores (M = 5.4) versus those who did not quit (M = 8.0), while among US participants the difference was not significant (Ms = 7.8 and 8.7, respectively). These results are consistent with the hardening hypothesis. They suggest that in countries with lower smoking prevalence such as the US, there may be less variability in depressive symptoms preceding a quit attempt, masking the impact of these symptoms on relapse. In contrast, countries where smoking is more common may have a larger proportion of smokers without significant depressive symptoms who may thus be able to more easily achieve abstinence. Taken together, we speculate that the higher rates of smoking observed in the European countries in the present trial compared with the US yields greater numbers of European smokers who can quit more easily. An alternative potential explanation for regional differences is the possibility of enrollment of "professional subjects" who participate in multiple clinical trials for financial gain, but do not adhere to study protocols.[46] The extent to which this varies regionally is not clear, but if such individuals were overrepresented in the US group relative to the EU group,[47] it could explain the apparent differences in cessation rate overall and in response to varenicline.

Findings indicated that, across regions, the advantage conferred by varenicline waned over time following discontinuation of the medication. Inspection of Figure 1 indicates that, for both regions, point prevalence abstinence declined between weeks 20 and 24, and stabilized thereafter. Notably, this roughly coincides with the transition from treatment to follow-up, and thus suggests a possible need for more intensive behavioral intervention during this phase. This potential need appears to be independent of level of depressive symptoms, as the three-way interaction including time, treatment condition, and MADRS was not a significant predictor of point-prevalence abstinence.

In contrast to two recent studies,[33,34] we found that women and men did not differ in terms of the impact of varenicline on either abstinence measure. For example, 16% of women in the placebo group and 33% in the varenicline group achieved 4-week continuous abstinence, rates generally consistent with the reports of McKee et al.[33] and Smith et al.[34] Given that previous reports were based on substantially larger samples, a plausible explanation is that the current study was underpowered to detect sex differences.

Our secondary analysis has several limitations. First, as was reported in the parent study,[14] we excluded participants with untreated or unstable depression along with a variety of other conditions (eg, bipolar disorder, current substance use disorders) that are frequently comorbid with major depression, limiting the generalizability of the results. Second, participants prescribed mood stabilizers and antipsychotics were also excluded, so we cannot comment on the effects of varenicline in depressed individuals taking those agents. Finally, attrition occurred across both treatment groups, thus, missing data could have affected results.

In conclusion, this secondary analysis of our previously reported randomized controlled trial demonstrates that varenicline aids smoking cessation in stably depressed patients even among those endorsing more depressive symptoms at baseline. Our results are consistent with a growing body of studies demonstrating that varenicline ameliorates nicotine withdrawal-related negative affect which interferes with successful quitting. Our findings also demonstrate that there are regional differences in smoking cessation rates and in the association between depressive symptoms and cessation which may reflect differences in the hardening of targets in the US versus Europe.

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Declaration of Interests

The study was funded by Pfizer, which was also involved in study design and data collection and analyses. Doran has no interests to declare. Anthenelli provides consulting and/or advisory board services to Pfizer, Arena Pharmaceuticals, and Cerecor and his institution has received research funding from Pfizer and Alkermes. Ms Dubrava is a Pfizer employee.

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